A Dissertation on

A STUDY ON THE EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Dissertation Submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

With partial fulfillment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE,

COIMBATORE

MAY 2019

Coimbatore Medical College

COIMBATORE, TAMILNADU, INDIA - 641 014

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

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Dissertation Topic	:	**A study on the extra articular manifestations of Rheumatoid arthritis**

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DECLARATION

I solemnly declare that the dissertation titled **"A study on the extra-articular manifestations of rheumatoid arthritis"** was done by me from JUNE 2017 to JUNE 2018 under the guidance and supervision of Professor **Dr. S.USHA. M.D.,**

This dissertation is submitted to **The Tamilnadu Dr.M.G.R.Medical University** towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

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ACKNOWLEDGEMENT

I wish to express my sincere thanks to our respected **Dean Dr. B. ASHOKAN M.S., MCH** for having allowed me to conduct this study in our hospital.

I express my heartfelt thanks and deep gratitude to the Head of the Department of Medicine Prof. **Dr. KUMAR NATARAJAN, M.D**. for his generous help and guidance in the course of the study.

I express my heartfelt thanks and deep gratitude to my guide **PROF.DR.S.USHA.M.D** for her support and guidance for the study.

I sincerely thank all professors and Asst. Professors- **Dr. S.AVUDAIAPPAN. MD**, Dr**. P.BALAMURUGAN. MD, Dr.ALAGUTHIYAGARAJAN.MD** for their guidance and kind help.

My sincere thanks to Department of RHEUMATOLOGY, RADIOLOGY, CARDIOLOGY, THORACIC MEDICINE, DERMATOLOGY, OPHTHALMOLOGY, PATHOLOGY and BIOCHEMISTRY for their help.

My sincere thanks to all my friends and post-graduate colleagues for their whole hearted support and companionship during my studies.

I thank all my **PATIENTS**, who formed the backbone of this study without whom this study would not have been possible.

Lastly, I am ever grateful to the **ALMIGHTY GOD** for always showering His blessings on me and my family

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CERTIFICATE – II

This is to certify that this dissertation work titled A STUDY ON THE EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS of the candidate DR.G.PONMOZHI with registration Number 201611311 for the award of M.D in the branch of General Medicine. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 2% (two percentage) percentage of plagiarism in the dissertation.

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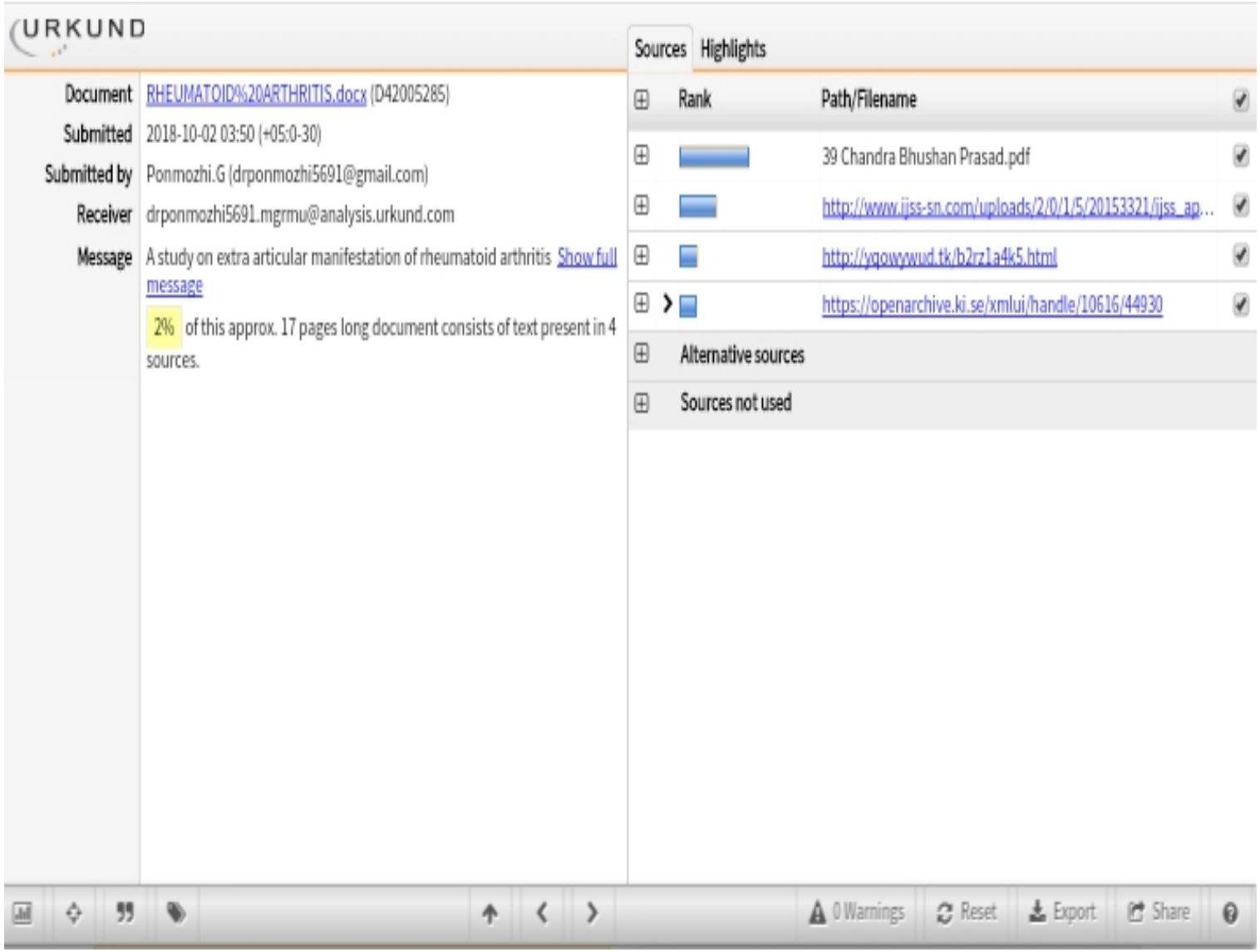
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ABBREVIATIONS:

AP view -Anteroposterior view

CRP - C-reactive protein

ESR - Erythrocyte sedimentation rate

HLA - Human leucocyte antigen

IFN -Interferon

IL -Interleukin

MCP -Metacarpophalangeal joints

MTP - Metatarsophalangeal joints

MHC -Major histocompatibility complex

PIP -Proximal interphalangeal joints

RA -Rheumatoid arthritis

EAM -Extra-articular manifestations

INTRODUCTION:

Rheumatoid arthritis is a chronic inflammatory and progressive disease characterized by various extra-articular manifestations. The presence of extra-articular manifestations of RA is associated with more severe disease, high rheumatoid factor levels and is considered a risk factor for early death in patients with rheumatoid arthritis. The presence of extra-articular manifestations may vary in different geographic areas and different ethnic groups. Extra- articular organ involvement includes skin, eyes, heart, lung, vasculitis, hematology etc. The presence of extra-articular manifestations is a major predictor of mortality in RA patients.(1)

This study focuses on the extra-articular manifestations in 100cases of rheumatoid arthritis attending outpatient department or admitted to ward at Coimbatore medical college hospital.

AIM OF THE STUDY:

- To investigate and compare the frequency and type of extra-articular manifestations
- To correlate the number of extra-articular manifestations with the duration of the study

In a well defined community based cohort of patients with rheumatoid arthritis

RHEUMATOID ARTHRITIS:

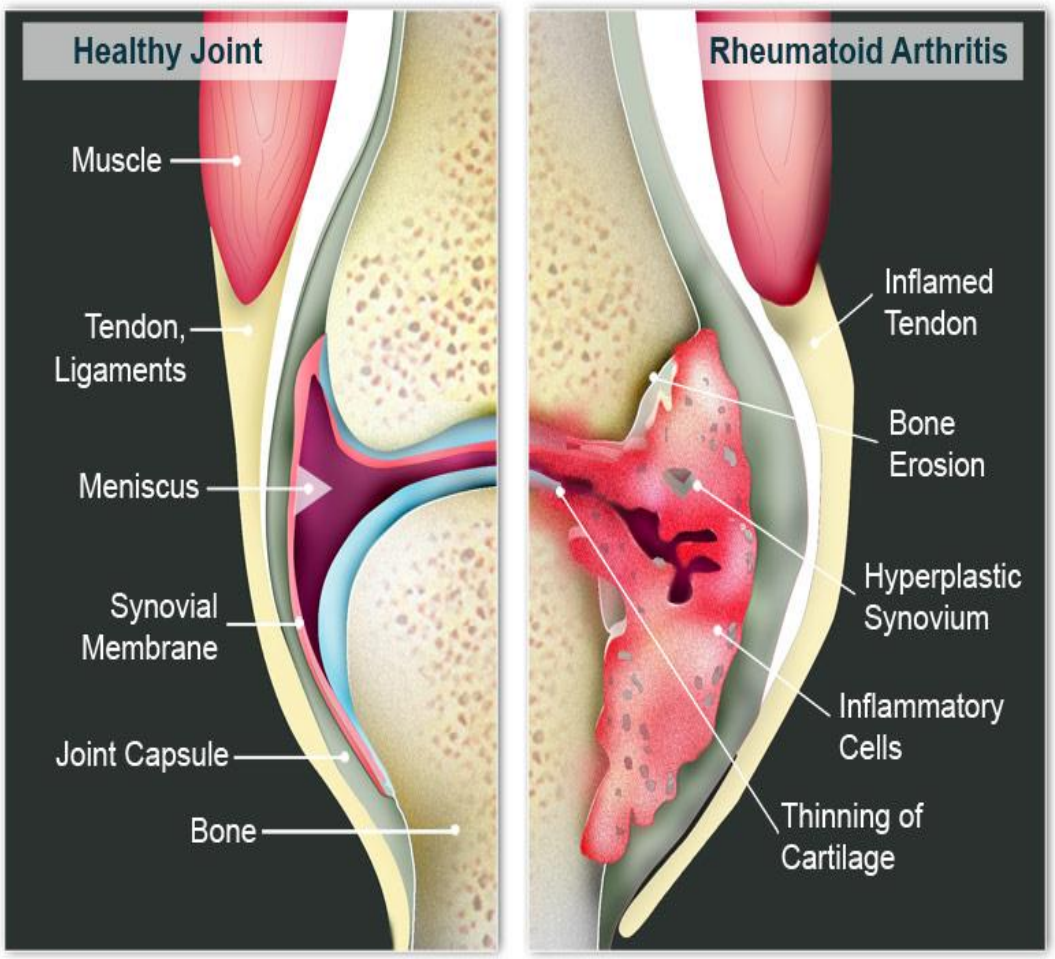
Rheumatoid arthritis (RA) is a chronic, destructive, inflammatory arthropathy manifested by articular and extra-articular features. RA has profound effects on patient function and morbidity and exacts a substantial economic burden on the affected persons.

Although the pathology of the synovial inflammation and cartilage destruction that occurs in patients with RA has been described for decades, many important developments in the understanding of genetic influences and immune pathophysiologic mechanisms have recently been defined. (1)

Basic research delineating the molecular mechanisms of synovial inflammation has driven the development of innovative therapies for patients with RA. Hopefully, new genomic and proteomic information will allow further stratification and identification of subsets of RA patients who respond better, longer, and with fewer adverse reactions to targeted therapies(1)

PATHOGENESIS:

Figure-1: Normal joint versus RA joint



The pathology of RA involves a complex interaction of three different scientific domains:

1) a complex genetic predisposition to the disease plus some environmental stimulus;

2) a self-perpetuating, self amplifying, intra-synovial immune response; and at the final stage, (2)

3) Tissue injury mediated by pro-inflammatory cells, inflammatory effector molecules, and derivative enzymes.

In individuals with RA, this process is orthotropic and produces a characteristic pathologic lesion in the synovium as well as the hallmark erosion of bone and destruction of cartilage at the joint margin.

The histopathology of RA synovium has been well described. The synovial lining, the interstitium, and the microvasculature are all involved. Early in the process, the synovial lining, which includes both Type A (macrophage-like) and Type B (mesenchymal or fibroblast-like) cells, becomes proliferative. The synovial lining increases in cell number and mass. Likewise, a diffuse and nodular inflammatory cell infiltrate is observed in the interstitium. It includes CD4+ and CD8+ lymphocytes, dendritic cells, and other antigen presenting cells. In some patients, the histologic appearance is quite dramatic, showing focal aggregation of both T- and B-cells, as well as the presence of germinal centers similar to that which is seen in lymphoid tissues. (2)

The synovium of the rheumatoid joint, although not malignant, often times behaves as a local invasive “tumor.” The microvasculature initially reveals endothelial cell activation. As the process matures, plasma cells and multinucleated giant cells appear, and the vascular supply becomes exuberant. Finally, the growing synovium appears as granulation tissue as it advances to the hyaline cartilage at the margin of the joint.(2) A

local effect of degradative enzymes and activated osteoclasts produces the classic erosion at the bone and cartilage margin. These enzymes may also affect structures that are more distant, including the tendons, ligaments, and other musculoskeletal structures. Erosions are produced by bone and matrix protein resorbing osteoclasts, which may be induced and activated by cytokines released into the inflammatory milieu.(2)

GENETICS AND ENVIRONMENTAL STIMULUS:

Genetic contributions for the pathogenesis of rheumatoid arthritis (RA) are very complex. Genetic studies in families of patients with RA suggest that monozygotic twins have a concordance rate for RA of between 15%-30%.

Certain alleles of the HLA-DR4 locus were found to be associated with RA in Caucasian patients. Most scientific evidence now suggests that certain genes within the major histocompatibility complex (MHC), located on the short end of chromosome 6 play the most significant role in the initiation of the rheumatoid disease .

Evidence also suggests that there are RA susceptibility genes on other chromosomes that appear to correlate with the phenotypic presentation of RA. Recently, allelic variations in PTPN22, a gene that encodes a tyrosine kinase involved in inhibition of T-cell activation, have been shown to be associated with RA.

Other factors are also involved in the triggering of RA in susceptible persons. One factor (not entirely extra genetic) is female sex. Particularly at younger ages of onset, RA is more common in women than in men, with a ratio of about 3:1. (2)

ROLE OF INNATE AND ADAPTIVE IMMUNITY:

A variety of genes and environmental factors contribute to susceptibility and pathogenesis of RA. The process of RA usually begins years before the onset of clinical features. This process usually involves breaking of tolerance and development of auto reactivity.

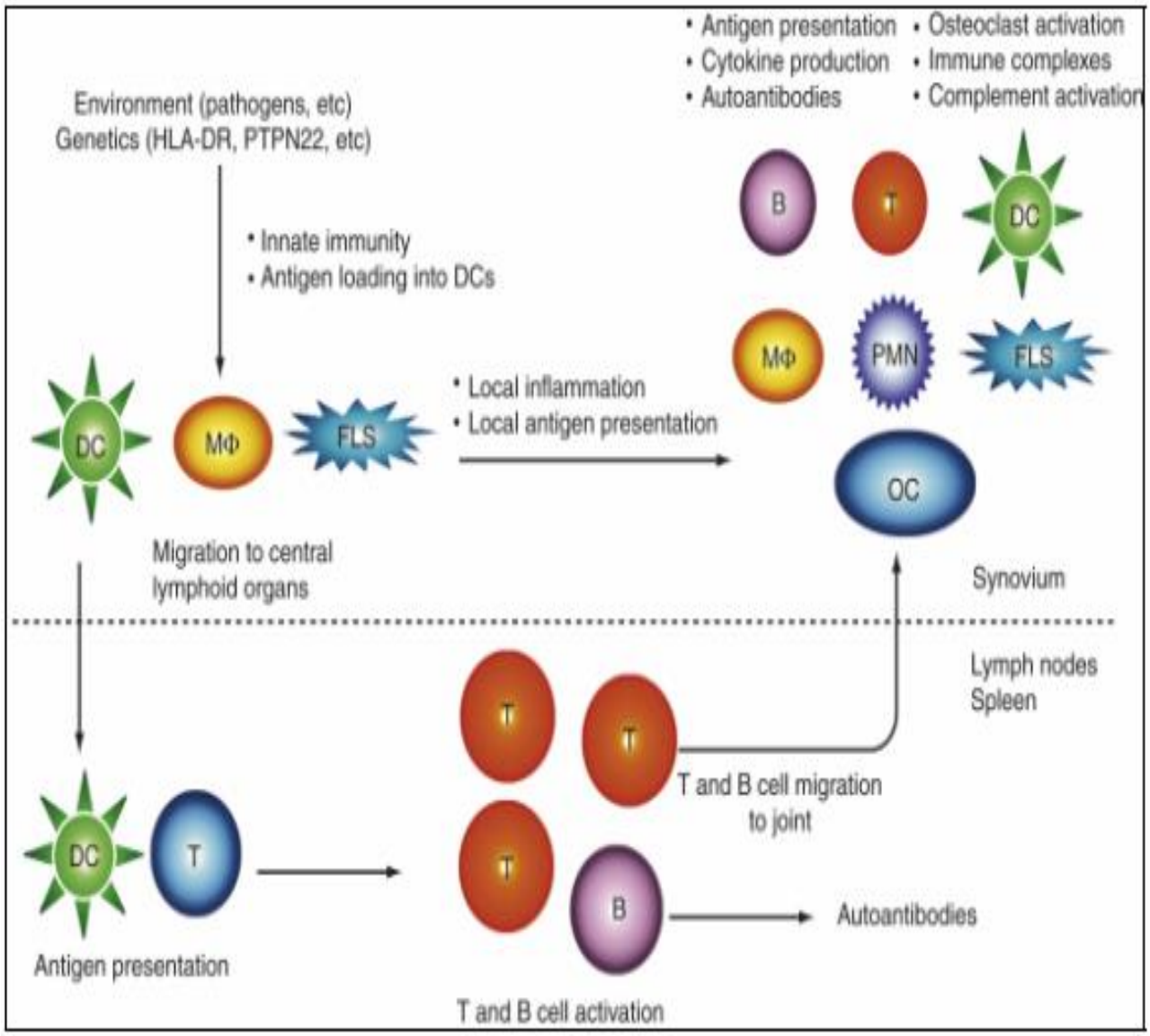
In the initial phases there is repeated activation of innate immunity. The innate immunity will activate fibroblast like synoviocytes, dendritic cells and macrophages in the initial phases in patients with hyperreactive immune system as evidenced by antibody production.

The individual genetic makeup including certain genetic polymorphisms and exposure to environmental factors both are needed. Chronic inflammation leads to protein citrullination at various sites including mucosal lining of lungs and joints.

Cigarette smoking bacterial products viral components can contribute to pathogenesis of RA.

Activation of innate immunity of synovial tissue causes increase in vascular leakage into the synovium production of chemo attractants that cause recruitment of immune cells into the joints and antigen processing by dendritic cells. (3)

Figure-2: Role of innate and adaptive immunity

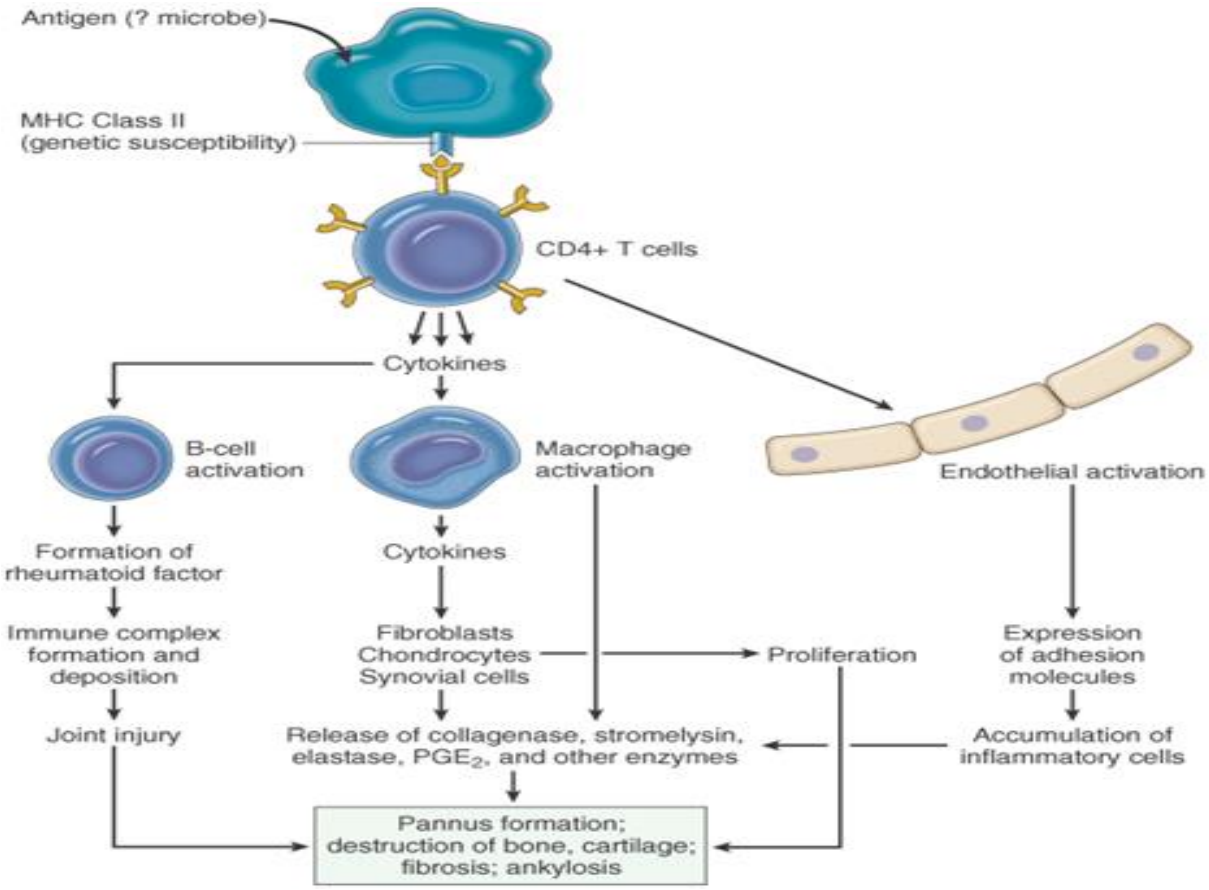


INTRA-SYNOVIAL IMMUNE RESPONSE:

The synovium in RA is marked by hyperplasia of intimal lining and sublining infiltration with mononuclear cells, especially CD4+Tcells, macrophages and B cells.

Intimal lining display unusually aggressive features. Macrophages in the intimal lining are highly activated and produce many cytokines (3). Lymphocytes can either diffusely infiltrate the sub lining or form lymphoid aggregates with germinal centres.Sublining CD4+T cells mainly display the memory cell phenotype. Synovial B cells and plasma cells in RA exhibit evidence of antigen-driven maturation and production.Dendritic cells can present antigens to T cells in synovial germinal centres.Mast cells produce small molecule mediators of inflammation.Neutrophils are rarely present in RA synovial tissue but can be abundant in synovial tissues(4)

Figure 3: Pathogenesis of RA:



EFFECTOR MOLECULES AND CARTILAGE DAMAGE:

Pro inflammatory cytokines plays an important role in etiopathogenesis of rheumatoid arthritis. The T cell mediated macrophage stimulation leads on to the release IL-1 and TNF-alpha. These cytokines are found circulating in the serum, synovial fluid. Both of these cytokines have broad biologic effects, including the induction by synoviocytes of matrix metalloproteinases as well as the inhibition of tissue inhibitors of metalloproteinase (TIMPs)(4)

In vivo and in vitro studies have documented that recombinant IL-1 and TNF-alpha injure normal hyaline cartilage. Chondrocytes, in particular, enter a catabolic phase when exposed to these cytokines, leading to an increase in collagenase production and a decrease in matrix protein synthesis (4).

TNF-alpha also induces adhesion molecules, e.g., the intra-cellular adhesion molecule 1 (ICAM-1), which may in turn affect the homing and trafficking of inflammatory cells into the synovium.

The “proof of concept” that TNF is an important mediator in the pathobiology of RA has been clearly shown by the profound clinical effects of the anti-TNF therapies (i.e., infliximab, etanercept, and adalimumab), on the signs, symptoms and structural damage that characterizes RA. Finally, the invasive nature of the RA pannus has suggested to some observers that the tissue behaves like a locally invasive tumor.

Indeed, growth factors such as TGF-alpha and FGF produced locally in the synovium by resident macrophages and fibroblasts may provide the drive for tissue expansion (4).

Certain autoantibodies are associated with RA. The most characteristic, certainly from a historical perspective is rheumatoid factor (RF). The landmark discovery of RF which is present in approximately 75%-85% of people with RA, marked the beginning of the understanding that RA is a systemic autoimmine disease(5). Although it is relevant to the diagnosis of RA, RF may be of greater value to the clinician in prognosis.

Epidemiologic observations suggest that the presence of the RF is a marker that predicts more serious disease. Rheumatoid factors are auto reactive antibodies that bind to the Fc portion of IgG molecules. RF is not specific for rheumatoid arthritis, as it is observed in a host of other autoimmune disorders or infectious diseases. Also, by definition of how the test is performed, 5% of the normal population will have a positive test for RF.

RF of isotypes indicative of class switching (ie, IgG and IgA, rather than IgM) may be more specific, as are higher titers. Although the potential contribution of RF to the pathogenesis of RA is unclear, it has been suggested that RF may induce tissue damage by acting as immune complexes.

Over the years, a variety of other autoantibodies have been reported to be associated with RA, including antikeratin antibodies, antiperinuclear factor, and

antifilaggrin antibody (5). It has been demonstrated that the antigen recognized in common by these antibodies is citrullinated protein.

Citrulline is a nonstandard amino acid created by the deamination of arginine residues in proteins by the enzyme peptidyl arginine deiminase (PADI). Interestingly, in some populations, allelic variations in the genes encoding PADI have been shown to correlate with RA.

Tests for anti-CCP (cyclic citrullinated peptide) antibodies are as sensitive as RF for the diagnosis of RA and are more specific. Similarly, high titers of anti-CCP antibodies define patients with a more aggressive disease phenotype.

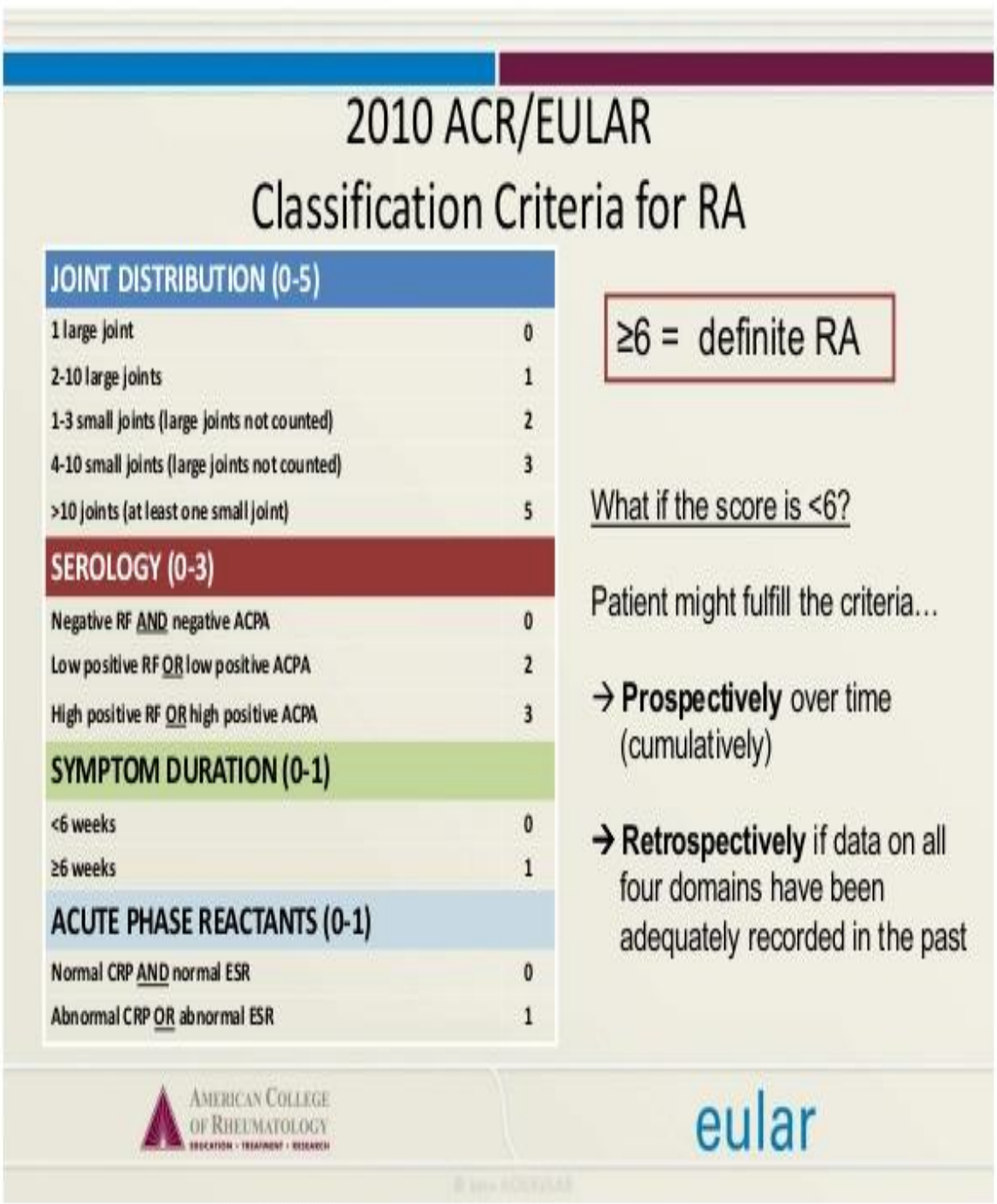
EPIDEMIOLOGY:

RA occurs worldwide in virtually all ethnic groups, with a prevalence estimated between 0.5% and 1%.

It is significantly more common in females than in males .

Death often results from infection, heart disease, respiratory failure, renal failure, or gastrointestinal disease rather than from joint disease itself. Whether this is due to an inflammatory process or due to exposure to antirheumatic drugs or both is unclear.(6)

CLINICAL FEATURES: Table:1 -ACR/EULAR classification criteria for RA:



Joint Manifestations:

Morning gel describes a peculiar stiffness that is pronounced in the morning or after periods of inactivity. It plagues most patients with active inflammatory arthritis, including those with RA. Its duration and quality often times provide the clues to early diagnosis of an inflammatory arthropathy.

The clinical hallmark of RA is a symmetrical polyarthritis involving the proximal interphalangeal joints (PIPs), metacarpophalangeal joints (MCPs), wrists, elbows, shoulders, hips, knees, ankles, and metatarsophalangeal joints (MTPs).

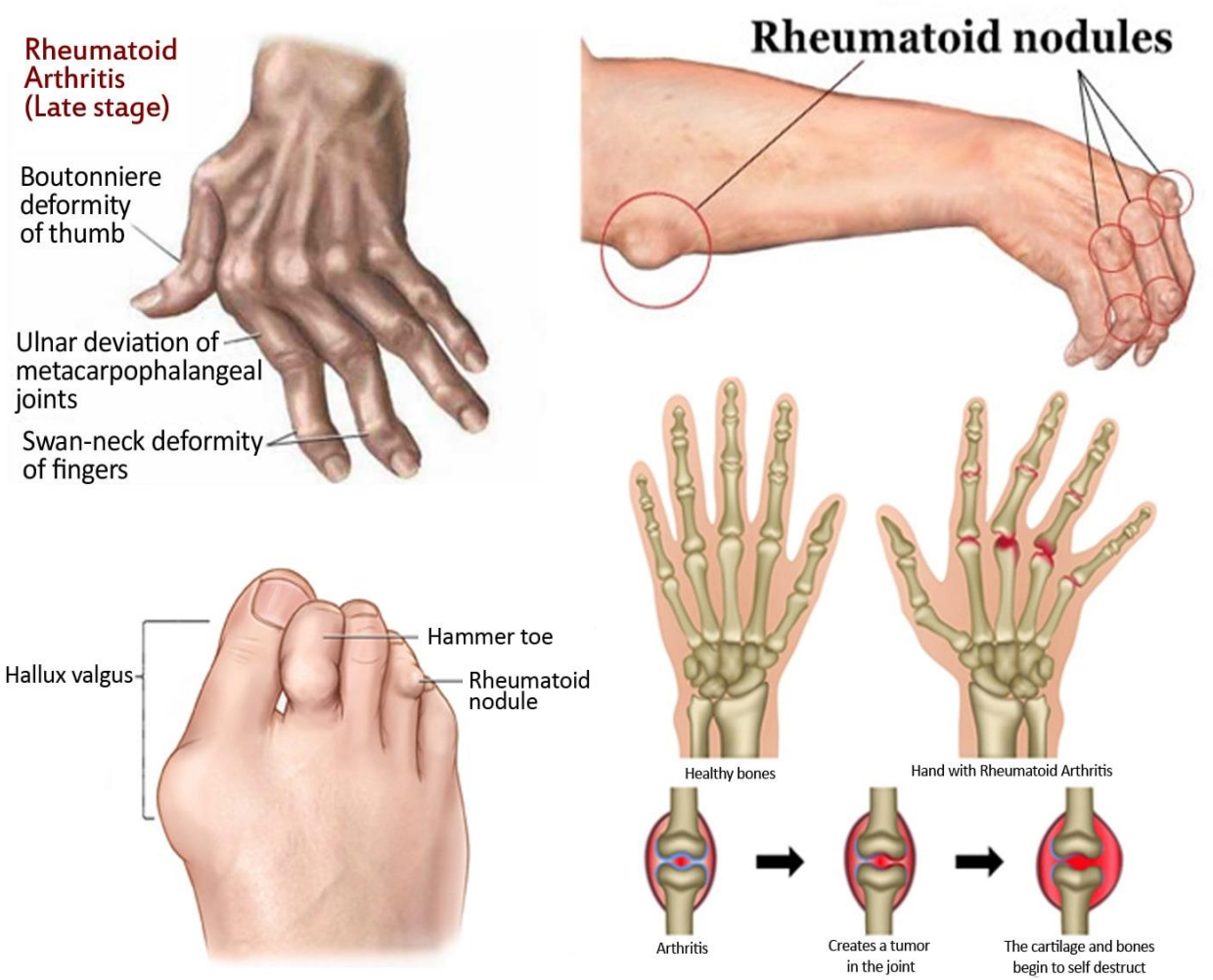
The hands and wrists are affected in approximately 90% of RA patients. Early in RA, joint tenderness and subtle swelling are observed, but after months to years the synovitis becomes proliferative and destructive.

The tissue within the joint becomes boggy to the touch, then typical joint deformities appear, including ulnar drift at the MCPs, rotatory subluxation at the wrist (ulnar styloid), and the "swan-neck" (flexion of DIP, hyperextension of PIP) and "boutonniere" (hyperextension of DIP, flexion of PIP) deformities. Most studies involving an inception cohort of patients suggest an overall, relatively linear rate of joint damage progression.

The development of erosions correlates with the persistence of inflammation, as evidenced by clinical measures of morning stiffness, synovial swelling, and elevation of erythrocyte sedimentation rate and other acute phase reactants.

Magnetic resonance imaging (MRI) visualizes and quantifies tissue or “synovial load” and also detects early invasion of pannus into hyaline cartilage and sub-chondral bone. There is also increasing interest in the use of ultrasonography, which can visualize bony erosions, joint fluid, and synovial hypertrophy.(7)

Figure 4: Articular manifestations of RA:



A syndrome of “pseudo-thrombophlebitis” can be seen in RA patients with active synovitis of the knee. Typically, a swollen, warm, tender calf causes problems with weight bearing, and the physical examination findings clearly mimic that of deep venous thrombophlebitis. (7)

SPINAL INVOLVEMENT:

The cervical spine is a common site of involvement in RA. In autopsy studies, up to 50% of patients with RA show some cervical spine involvement. There is a direct relationship between cervical spine disease and the presence of erosive peripheral joint disease.

Proliferative synovitis can damage the ligaments and articular cartilage of the cervical spine, causing several types of cervical spine instability. These include:

1) atlantoaxial subluxation in 50%-70% of patients;

2) subaxial subluxation in 20%-25% of patients; and

3) basilar invagination into the foramen magnum alone or in combination with atlantoaxial subluxation in approximately 20% of patients.

Symptoms of cervical spine involvement in RA include neck pain, occipital headache, and paresthesias in the extremities. (8)

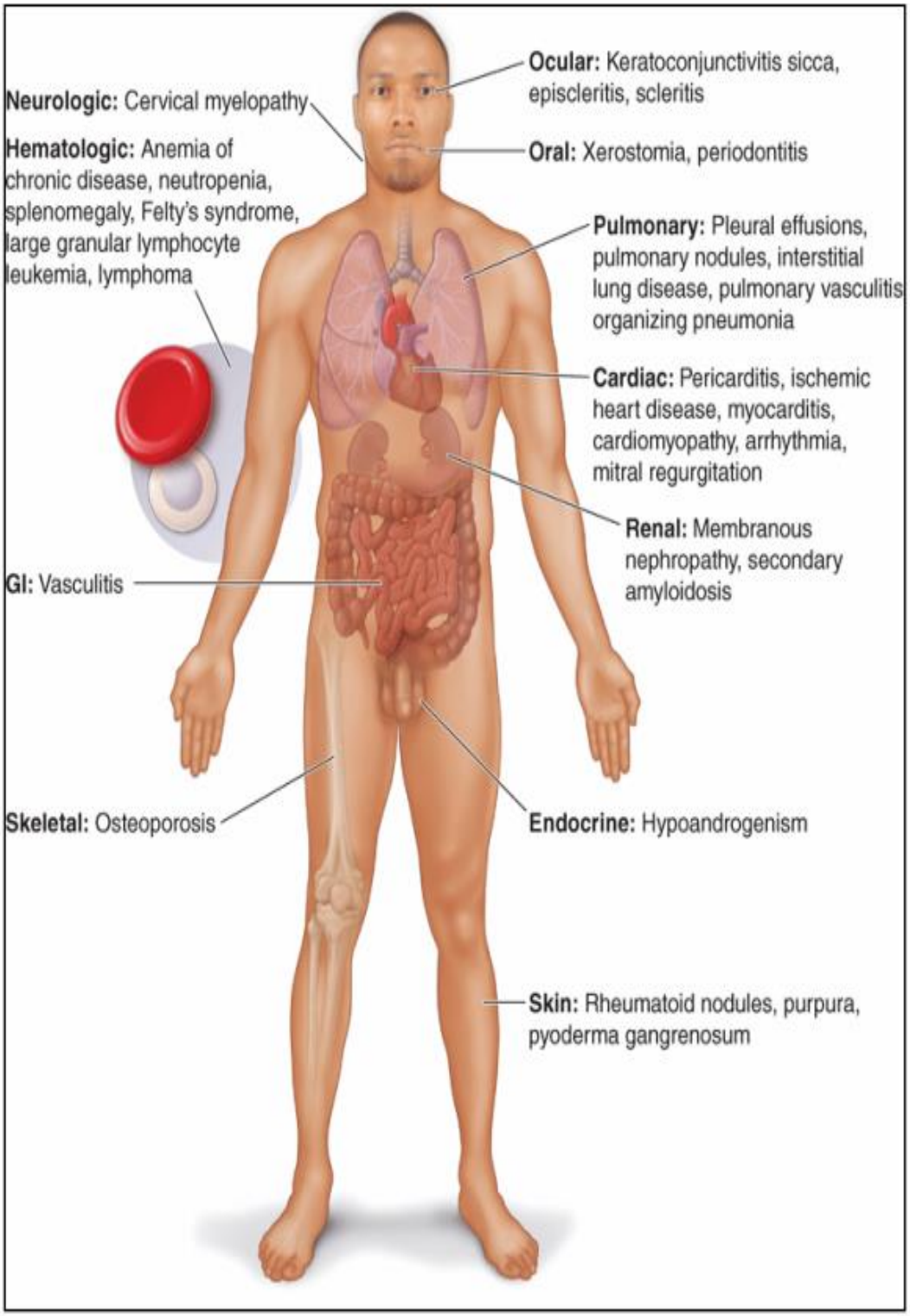
EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Table 2: Extra-Articular Manifestations of Rheumatoid Arthritis[10]

Organ System	Systemic Manifestation
Cardiovascular	Coronary artery disease, pericarditis, conduction defects, aortic root dilatation
Hematologic	Anemia, thrombocytosis, Felty's syndrome, large granulocytic leukemia, non-Hodgkin's lymphoma
Pulmonary	Pleural effusion, nodules, interstitial lung disease
Vascular	Vasculitis, neuropathy
Bone	Osteopenia and osteoporosis
Ocular	Keratoconjunctivitis sicca, scleritis, episcleritis, peripheral ulcerative keratitis
Salivary glands	Secondary Sjögren's syndrome with dry eyes and mouth
Skin	Cutaneous vasculitis, nodules, pyoderma gangrenosum

FIGURE: 5

Figure-5:



Pleuropulmonary manifestations:

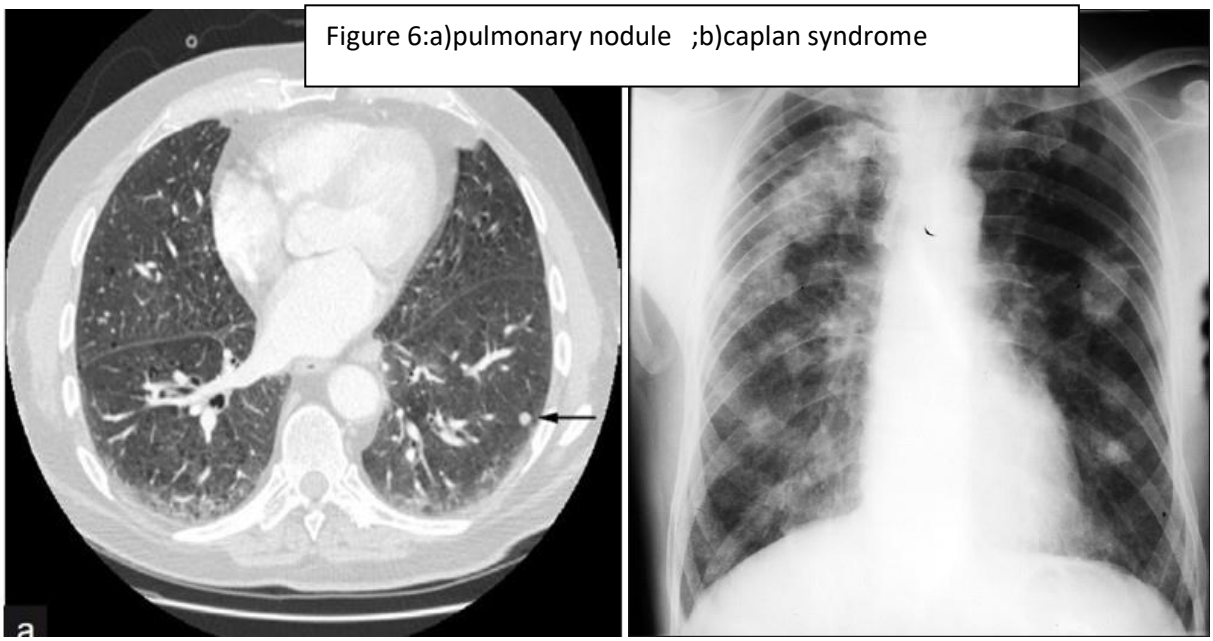
Abnormalities of the pleura and lungs have been detected by high-resolution omputed tomography (HRCT) in up to 75% of patients with RA. However, pleura inflammation is often asymptomatic and may not be detected until chest radiographs are done for other reasons. The prevalence of pleural effusion in RA is only about 5%. In some patients the pleural fluid glucose may be dramatically low compared to serum levels. Although it may present rarely before arthritis is manifested, pleural effusion usually occurs in individuals with active established RA. About one-third of patients with RA with pleural effusions have coexisting interstitial lung disease.(8)

Interstitial pulmonary fibrosis occurs in 20%-40% of patients with RA, more commonly in patients with rheumatoid nodules and serum rheumatoid factor. It can be asymptomatic in its early stages because the decreased physical activity of patients with RA may be insufficient to induce dyspnea. The early radiographic changes of interstitial pulmonary fibrosis, consisting of ground-glass opacities predominantly in the lower lungs, may not be evident on conventional plain radiographs but appear as high-attenuation lesions at the periphery of the lungs on HRCT. Compared to HRCT, pulmonary function testing, especially assessment of residual volume, is a more sensitive but relatively nonspecific indicator of interstitial pulmonary fibrosis in RA. Interstitial lung disease in patients with RA may also be a complication of gold or methotrexate therapy, and there have also been anecdotal reports associated with the TNF inhibitors.(8)

Because transbronchial biopsies do not provide enough tissue for reliable diagnosis, the pattern of lung disease in patients with RA for whom treatment for pulmonary symptoms is being contemplated is best determined by open-lung biopsy. Various histologic patterns have been described, including pulmonary rheumatoid nodules, usual interstitial pneumonitis (UIP), bronchiolitis obliterans with patchy organizing pneumonia (BOOP), lymphoid hyperplasia, and cellular interstitial infiltrates. Patients with rheumatoid nodules, lymphoid hyperplasia, or non-specific cellular interstitial infiltrates have a better prognosis than patients with UIP.

Pulmonary rheumatoid nodules may occasionally be visualized on routine radiographs and confused with malignancy. Occasionally, these nodules may cavitate. The unique entity of Caplan's syndrome defines multiple pulmonary nodules with cavitation in coal miners exposed to dust and other inhalants

Figure 6:a)pulmonary nodule ;b)caplan syndrome



Cardiac Manifestations:

Symptomatic cardiac involvement is rare in patients with RA; however, echocardiography has shown the prevalence of asymptomatic cardiac involvement to be higher than previously reported in autopsy studies. In a study of patients with RA and no cardiac symptoms, there was a significantly increased prevalence of posterior pericardial effusion (57.1%), mitral valve prolapse (34.3%), mitral valve thickening (22.9%), aortic root dilatation (34.3%), and aortic valve thickening (20.0%) compared to healthy persons.

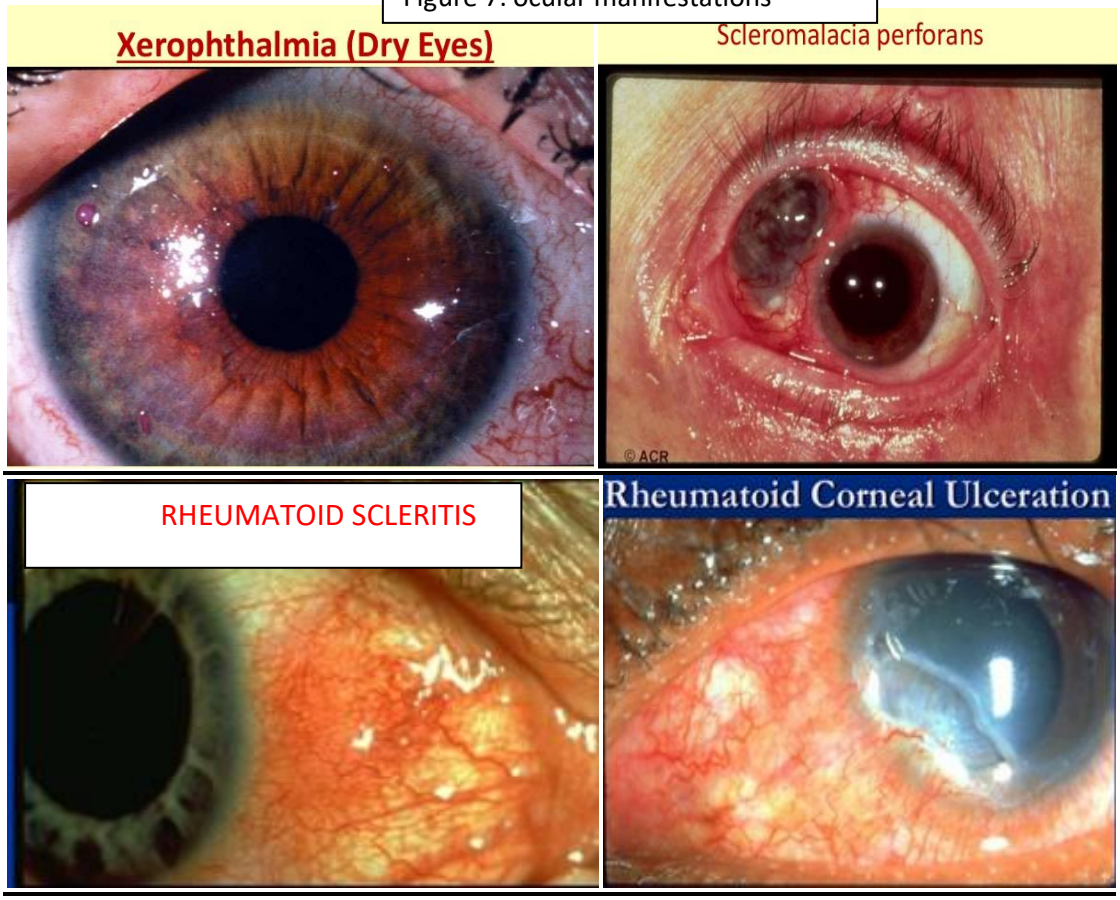
Myocarditis and endocarditis are not commonly seen in patients with RA. Areas of focal myocarditis are seen at autopsy but are clinically insignificant. Arrhythmias secondary to involvement of the conduction system by myocarditis, vasculitis, or nodules can occur but are exceedingly rare. Endocardial disease in the form of nonspecific valvulitis has been observed in up to 70% of autopsied cases but is usually asymptomatic and generally goes unrecognized during life. Rarely, valvular dysfunction may be caused by rheumatoid nodules. Aortitis, most commonly involving the thoracic aorta, was identified in 10 of 188 consecutive autopsied cases of patients with RA(**8)**

Ocular manifestations :

The most common ocular manifestations is scleritis ,associated with anterior uveitis or ulcerative keratitis or corneal melt .There is mononuclear infiltrates in the eye leading to production of inflammatory cytokines .Ocular manifestations can predate arthritis occurrence and is independent predictor of disease activity.(9)

There is also occurrence of secondary Sjogrens syndrome causing keratoconjunctivitis sicca. RF levels correlate with keratoonjunctivitis sicca.

Figure 7: ocular manifestations



DERMATOLOGICAL MANIFESTATIONS:

Rheumatoid nodules are the most common specific cutaneous manifestation in patients with RA. Rheumatoid papules are an additional characteristic cutaneous manifestation associated with RA. The histological features include leukocytoclastic vasculitis and palisading granuloma with collagen degeneration. Pyoderma gangrenosum can also occur. Rheumatoid vasculitis may at times difficult to diagnose because of the

wide variations of clinical presentations. Chronic leg ulcers with or without edema are often documented in patients with RA. (9)

The other dermatological manifestations include skin atrophy, transparent skin, generalized hyperpigmentation, hyperhidrosis of the patients, erythema nodosum ,alopecia, vitiligo, urticaria, tylosis, ingrowing nail (9)

Figure 8:a)purpura

b) atrophic skin with purpura

c)Methotrexate induced vasculitis

Various nail abnormalities thickening, discoloration, splinter hemorrhages, longitudinal nail beading, curvature abnormalities, and surface abnormalities.

Hematological manifestations:

A mild normocytic normochromic anaemia occurs in patients with rheumatoid arthritis .It correlates with elevation of ESR and disease activity. The causes of anaemia in RA is mixed.

Thrombocytosis also occurs in RA. There has been a significant correlation between thrombocytosis and extra-articular manifestations of RA and disease activity.

Eosinophilia also occurs in some patients .Paraproteinemia is associated with poor outcome in rheumatoid arthritis.(10)

Felty's Syndrome and Pseudo-Felty's Syndrome:

Felty's syndrome, which was reported in previous years in as many as 1% of patients with RA, was originally described as the association of RA with leukopenia and splenomegaly. It was frequently associated with the presence of rheumatoid nodules, Sjögren's disease, and other extra-articular manifestations. (10)

Felty's syndrome typically occurred in older patients with advanced erosive RA of at least 10 to 20 years' duration. Almost all Caucasian patients with Felty's syndrome were positive for HLA-DR4. Serum rheumatoid factor is almost always present, usually in high titer, and antinuclear antibodies (most commonly antihistone antibodies) are present in 47%-100% of patients with Felty's syndrome.

RA is the disease most frequently associated with the LGL syndrome (up to 39% of patients). Patients with the LGL syndrome and RA exhibit idiopathic neutropenia and splenomegaly, a condition called pseudo-Felty's syndrome. Because of an increased number of LGLs, the total leukocyte count may be normal in patients with pseudo-Felty's syndrome.(10)

Similar to patients with Felty's syndrome, patients with pseudo-Felty's syndrome have serum rheumatoid factor and other autoantibodies and are susceptible to frequent infections.

VASCULITIS:

Initially there is an inflammation of medium and small blood vessels. One of the most dreaded complication of RA is systemic rheumatoid vasculitis.(11)

Risk factors include male gender, long standing disease, high titre RF in serum, hypocomplementemia, erosive disease, circulating cryoglobulin, deposition of immune complex and complement in blood vessels and extra-articular features such as subcutaneous nodules.

The presentations include

1)distal arteritis- splinter hemorrhages ,nail fold infarcts

2)cutaneous ulceration–pyoderma gangrenosum

3)peripheral neuropathy in the form of mononeuritis multfilex or sensoryneuropathy

Figure 9:RA vasculitis

Rheumatoid Nodules:

Rheumatoid nodules occur in approximately 15% to 40% of patients with RA and are associated with the presence of serum rheumatoid factor, erosive joint destruction, necrotizing vasculitis, and other extra-articular manifestations of RA. (12)

They usually occur in areas that are repeatedly subjected to friction or pressure, such as the extensor surface of the forearm or the Achilles tendon; however, nodules may also develop in viscera such as the heart and lungs.

Figure:10 –Rheumatoid nodules

These nodules are usually smaller than 5 mm and are located on the fingers, although they may be present at other sites(12)

Histologically, rheumatoid nodules contain a central area of necrosis encircled by palisading histiocytes, which are surrounded by granulomatous tissue infiltrated with lymphocytes.

Malignancy:

The overall incidence of cancer in patients with RA is not increased; however, patients with RA have an increased risk of developing lymphomas and lung cancer, and a decreased risk for developing cancers of the colon, rectum, and stomach. The low risk of colorectal cancer among RA patients may be related to their common use of nonsteroidal anti-inflammatory drugs (NSAIDs).(12)

Patients receiving methotrexate therapy for RA have developed non-Hodgkin's lymphoma, which may regress with the discontinuation of methotrexate therapy, as occurs with lymphomas in patients receiving immunosuppressive drugs after organ transplantation. These reversible lymphomas are usually diffuse, large-cell lymphomas of B-cell lineage.(13)

Epstein-Barr virus genome and latent membrane protein have been detected in lymphomas of patients with RA who were treated with methotrexate alone or with cyclosporine A, suggesting that immunosuppression may have contributed to the development of these lymphoid neoplasms. (13)

Recently, there has been some concern as to whether patients treated with TNF inhibitors may be at greater risk of developing lymphomas, particularly non-Hodgkin's lymphoma (NHL). Analysis of any increased risk attributable to therapy is compounded by the fact that patients with severe RA are at greater risk of developing NHL than the general population, and the risk correlates with the severity and activity of disease. Of note, this has been the subset of RA patients for whom TNF inhibitor therapy has been

most widely utilized. At present, it seems that much of the increased risk observed among patients treated with TNF inhibitors relates to the activity and severity of RA, but this bears close observation.(13)

Prognosis:

The clinical expression of RA is usually established in the first 2 years, although the disability measures almost always get worse with time. As mentioned previously, mortality studies suggest that patients with severe RA die at an accelerated rate due to infection, cardiopulmonary disease, and gastrointestinal bleeding.

Results from a recent observational study suggest that patients who are unresponsive to methotrexate may have a significantly higher mortality risk compared to those patients who do respond to methotrexate. The presence of serum rheumatoid factor in patients appears to best predict the subsequent development of RA for patients presenting with undifferentiated polyarthritis. Patients who have elevated titers of serum rheumatoid factor and anti-CCP antibodies early in the course of disease more often develop erosive joint disease than patients who are seronegative. High titers of rheumatoid factor are also associated with the appearance of extra-articular manifestations. Likewise, RA patients who have the HLA-DR4 haplotype usually have a poorer clinical outcome.(14)

Most patients with RA have a slowly progressive course characterized by exacerbations and improvements. Long-term studies have shown that fewer than 10% of patients with RA ever go into a prolonged remission. Greater number of tender or

swollen joints at disease onset has been correlated with increased disease activity and joint erosion. Lower socioeconomic status and fewer years of formal education, which is a component of or a surrogate marker for lower socioeconomic status, have been associated with higher morbidity and mortality in RA.(14)

Defining markers of a bad prognosis early on in RA facilitates therapeutic decision-making. Historically, second-line therapy was reserved for severe refractory patients who had unremitting disease for years. With recent evidence suggesting that erosions appear early, there is a new emphasis on treating RA patients earlier with second-line agents. Bad prognostic features include: RF and anti-CCP seropositivity; elevated markers of inflammation (ESR and CRP); rheumatoid nodules; extra-articular features; larger numbers of active joints; early functional impairment; and early appearance of erosions. (15)

Therapy:

Although RA treatment approaches are highly individualized, according to practitioner experience and patient preference, several trends deserve mention. Controlling pain is a critical objective, but RA with active inflammation needs to be differentiated from the mechanical pain that can arise with joint deformity, because management strategies will differ.(16)

Treatment algorithms should always be used as a guideline to be modified by the actual clinical circumstances not as a rigid treatment protocol. The critical step in

determining treatment guidelines involves differentiating slowly progressive from aggressive disease (16)

Treatment strategy:

A study in early RA from the Netherlands has provided some insight as to the relative efficacy of various treatment approaches. In this study, known as the Best trial, 508 patients with early RA (defined as < 2 years of arthritis) were randomized to one of 4 treatment arms:

1) sequential monotherapy (beginning with methotrexate [MTX]);

2) step-up combination therapy (also beginning with MTX);

3) initial combination therapy with MTX, sulfasalazine (SSZ) and high dose prednisone (as was used in the earlier COBRA study); and

4) initial combination therapy with MTX plus TNF-inhibitor (infliximab). In all arms, the goal was low levels of disease activity. At their 3 monthly follow up visits, patients not achieving this goal, defined by a disease activity score (DAS) of 2.4 or less, were required to have their treatment altered according to an algorithm specific for each group. Eventually, groups 1, 2, and 3 could end up on MTX plus TNF inhibitor. If patients did achieve low disease activity on 2 successive visits, treatment was tapered (to a minimum of MTX 10 mg/week over the first 2 years, and off all therapy after the second year). Data from the 1 year and 2 years of follow-up showed that patients in groups 3 and 4 achieved low disease activity and even remission quicker than did those in

groups 1 and 2, although as might have been expected given the study design with its mandatory changes in therapies, clinical efficacy was comparable across all groups by 2 years. (14)

However, the progression of joint damage measured radiographically was less in groups 3 and 4 through the first 2 years of the study. Preliminary assessment at year 3 has suggested that a substantial number of patients can have their therapy tapered or even discontinued while maintaining low levels of disease activity. This suggests that early aggressive therapy may be able to change the course of the disease.(14)

Specific Antirheumatic Drugs:

NSAIDs and Salicylates:

NSAIDs inhibit the production of prostaglandins of the E series, including the formation of prostacyclin and thromboxane, resulting in complex effects on vascular permeability and platelet aggregation. NSAIDs specifically inhibit cyclooxygenase activity and thereby reduce the conversion of arachidonic acid to PGG2.thereby reducing pain and swelling. However they do not retard joint destruction.

Glucocorticoids:

Glucocorticoids have profound anti-inflammatory effects caused by the suppression of immunomodulating proteins, including IL-1, IL-6, TNF- , interferon-gamma, and GMCSF. In addition, glucocorticoids inhibit the production and expression

of pro-inflammatory prostaglandins and leukotrienes, inducible nitric oxide synthase, plasminogen activator, and adhesion molecules (ICAM-1). Glucocorticoids also modulate cellular physiology by reducing neutrophils at sites of inflammation; decreasing the number and function of monocytes ,macrophages (perhaps by affecting chemokine physiology); suppressing antigen presenting cells; and inhibiting the number of circulating lymphocytes and their functions, including the proliferative response to mitogens, cytokine production, and immunoglobulin production. In addition, glucocorticoids also produce significant metabolic effects elsewhere.

Clinical use: Low dosages of glucocorticoids coadministered with NSAIDs and DMARDs are used routinely as "bridge therapy" for some patients with very active RA. In that setting, the plan is to first quickly extinguish the signs and symptoms of the "flare" phenomena, but then to always taper glucocorticoid treatment once the DMARD takes effect. In some patients with chronic progressive disease, long-term low-dose glucocorticoid treatment is required to maintain the disease at a certain level of control and to secure a reasonable quality of life. Glucocorticoids are also used intermittently over 1-2 weeks in doses tapering rapidly from 20 mg per day for patients experiencing a "flare" of RA. Glucocorticoids in high doses is used for treatment of ILD. Intra-articular injection of triamcinolone is used for one or few actively inflamed joints.

Acetaminophen:

It has analgesic and antipyretic properties. The exact mechanism of action is unknown, but it may have both peripheral and central actions. Acetaminophen is used routinely in RA patients to manage pain due to mechanical joint problems.

DMARDs

Antimalarial Drugs:

These drugs are used in early RA (usually before methotrexate, parenteral gold, and anticytokine therapy), or in more aggressive RA as combination chemotherapy with methotrexate. A recent controlled trial of hydroxychloroquine showed it to be significantly more effective than placebo in patients with early RA. Clinical effects are usually observed at 8 to 12 weeks; starting dosage is 400 mg/d in divided doses, with a dose reduction to 200 mg/d at 8 to 12 weeks if a good response is observed.

Sulfasalazine:

Sulfasalazine has been used in patients with early mild RA, and long-term studies suggest a favorable efficacy profile. Recently, it has also been shown to be marginally effective in seronegative spondyloarthropathies, especially among those with psoriatic arthritis. But it has little effect on patients with axial spine disease. It is commonly prescribed as part of combination therapy with hydroxychloroquine and methotrexate. The initial dose is usually 500 mg twice a day, with gradual increase to a total of 3 g/d in two divided doses.

Methotrexate:

It is considered as the gold standard second-line antirheumatic drug against which other drugs are usually compared.(17) The newer TNF inhibitors are usually added to "partial responders" of methotrexate or after failure with methotrexate or it has caused toxicity.

In RA patients, it may not function as it does in patients with malignancy receiving antimetabolite chemotherapy. Evidence suggests inhibition of inflammation as a potential mechanism of action. However, methotrexate it will not cause inhibition of cyclooxygenase. It causes inhibition of IL-1 and leukotriene-4 (LTB4), and reduces levels of proteolytic enzymes(18)

It is also useful in the treatment of spondyloarthropathies, systemic vasculitis, and nonrenal SLE. But it is most extensively studied in RA patients. In most studies, methotrexate induces a predictable response at 6 to 8 weeks, peak occurs at 6 months and then it requires progressive increase in dosage of the drug in order to maintain the improvement. (18)

The major side effects include hepatotoxicity. In patients with RA, mild elevation of liver enzymes that is transient commonly observed, but cirrhosis, is extremely uncommon. (19)

Bone marrow suppression causing pancytopenia is an uncommon but clinically important adverse event in RA patients on methotrexate therapy. Renal insufficiency

resulting in increased drug levels and leading to prolonged exposure to methotrexate may cause predisposition to marrow failure(19)

Cyclosporine:

Cyclosporine causes inhibition of interaction between T-cell and macrophage thereby reduces synthesis of IL-2,and prevents IL-1 receptor production, and it suppresses the synthesis and release of IL-2 by CD4+cells. Recent studies also show that cyclosporine causes increase in insulin–like growth factor levels and bone GLA (gamma-carboxyglutamic acid) protein and it may cause stimulation of the androgen axis(20). Cyclosporine does not inhibit the growth of bone marrow-derived B-lymphocytes, myeloid series and erythroid cell lines .(20)

. Use of cyclosporin A in rheumatologic conditions has thus far included RA, Sjögren's disease, Behçet's-related inflammatory eye disease, SLE, scleroderma, polymyositis, and systemic vasculitis. Dosages of <5 mg/kg daily reduce potential for side effects. A number of combination therapy studies have been reported, among them a study comparing the use of cyclosporine A to placebo in RA patients who were inadequately controlled with low-dose weekly oral methotrexate. (21)This study showed a significant drug effect compared to placebo, although concerns about this continue. However, because of the potential for adverse reactions even at the lower doses, cyclosporine A use is decreasing as the anti-TNF inhibitors penetrate routine practice.(22)

Leflunomide:

It was initially developed to prevent transplant rejection; it was developed clinically for RA patients as an alternative therapy to methotrexate and sulfasalazine. Its active metabolite inhibits dihydroorotate dehydrogenase, thereby it interferes with synthesis of pyrimidine. (23) In the downstream it causes inhibition of activated T-cells and B-lymphocytes and other cells participating in the process of inflammation. It causes inhibition of T-cell proliferation and B-cell antibody production. Tyrosine kinase is also inhibited by leflunomide .In clinical practice, it use is increased particularly among patients who has failed to respond to methotrexate or who were not suitable candidates for treatment with anticytokines.(24)

Tumor Necrosis Factor Inhibitors:

Etanercept:

It is a dimeric fusion protein of the extracellular p75 soluble TNF-alpha receptor which is linked to IgG1. Etanercept specifically binds to TNF-alpha and thereby preventing its interaction with the TNF-alpha receptor. It is given subcutaneously, at a dose of either 25 mg twice per week or at a dose of 50 mg once a week. Similar to all TNF inhibitors, it has potential for causing immune suppression and increased risk of infection. (25)

Infliximab:

It is a chimeric IgG1 monoclonal antibody directed against TNF-alpha, thereby it causes inhibition of its biologic effects in the synovial tissue. It is given intravenously, and following a single intravenous administration of 3 mg/kg, its half-life is 8 to 9.5 days. Infliximab has been approved for use, along with methotrexate, at a dose of 3 to 10 mg/kg given once in 4 to 8 weeks (26). The usually used regimen is 3 mg/kg by intravenous infusion at 0, 2, and 6 weeks, followed by 3 mg/kg intravenously every 8 weeks. Adverse effects include increased bacterial, fungal infections, latent TB reactivation, increased risk of lymphoma, drug induced lupus and neurological deficits

Adalimumab:

It is a human IgG1 monoclonal antibody directed against TNF-alpha that specifically binding circulating and cell-bound TNF, thereby it inhibits its biologic effects. It is given subcutaneously and its half-life is approximately 13 days. It is administered at a dose of 40 mg every alternate week. (27)

Anakinra:

Interleukin-1 (IL-1) which is a pro-inflammatory cytokine that contributes to inflammation of the synovial tissue, also by the induction of other inflammatory cytokines and induction of protein degrading enzymes such as collagenase. It is a

homologue of the naturally occurring antagonist of IL-1 receptor that competes with IL-1 for binding to type 1 IL-1 receptors. (28)

Anakinra is administered as a daily subcutaneous injection. It has a half-life of approximately 4-6 hours. It has been found to be effective in several double blind placebo controlled trials. In general, responses observed with anakinra is less than that seen with TNF inhibitors (28)

Infections are important side effects due to active pro-inflammatory nature of IL-1. In a study in which used anakinra in combination with the TNF inhibitor etanercept, a greater number of serious infections developed; therefore, combination therapy is not recommended nowadays

Abatacept:

It is a T-cell costimulation inhibitor, known as CTLA-4-Ig previously. (29)Abatacept is a fusion protein that consists of the extracellular portion of the T-cell molecule CTLA-4 connected with human IgG1 Fc portion so that will not activate complement. CTLA-4 which is a natural inhibitor of the interaction between CD28, and its ligands CD80 and CD86 which is present on antigen presenting cells. It is given as an intravenous infusion over a time of 30 minutes once in a month, following an initiation treatment phase at weeks 0, 2 and 4. The dose of abatacept is weight based, approximately 10 mg/kg. The efficacy of abatacept has been proven in patients with RA

with active disease inspite of concurrent MTX or who has failed to respond to previous treatment with TNF inhibitors. (29)

Rituximab:

It is a chimeric monoclonal antibody which is directed against CD20, which is expressed on B-cells. Thereby causing B-cells depletion thereby leading to reduction of inflammatory process. It has been approved for treatment of refractory RA together with methotrexate and appears to be more effective in the treatment of seropositive cases when compared with seronegative arthritis. Side effects of Rituximab include mild to moderate infusion related reactions, infections and risk for development of progressive multifocal leukoencephalopathy is very low. (30)

Tocilizumab:

It is a monoclonal antibody directed against IL-6 receptor.IL-6 being a proinflammatory cytokine has role in causing inflammation of joints and damage.

It has been associated with an increased risk of infection, neutropenia, and thrombocytopenia (33)

Tofacitinib:

It is a small-molecule inhibitor that primarily inhibits JAK1 and JAK3, which mediate signaling of the receptors for the common gamma chain related cytokines1L-2,IL-4,IL-7,IL-9,IL-15 and IL-21.Tofacitinib in randomized clinical trials has been shown to improve the signs and symptoms of RA significantly over placebo.

MATERIALS AND METHODS:

SOURCE OF STUDY:

Primary data collected by me from the cases of rheumatoid arthritis attending out - patient department of Rheumatology at Coimbatore medical college hospital

DESIGN OF STUDY: Descriptive study

PERIOD OF STUDY: One year

METHODOLOGY:

This is a descriptive study on the extra -articular manifestations of RA in 100 cases of rheumatoid arthritis attending out-patient department or admitted in the medical ward of Coimbatore medical college hospital ,Coimbatore from June 2017 to June 2018.Patients who have been already diagnosed with RA were retrospectively evaluated from the hospital records. All these patients were subjected to complete medical history and physical examination, complete blood count, urine analysis and blood biochemistry by using a well structured pro-forma.The diagnosis of extra-articular manifestations will be confirmed by peripheral smear, chest radiography, pulmonary function tests, CT chest, ophthalmic examination, ECG, Echocardiography and skin biopsy if skin manifestations are present. The overall frequency of extra-articular manifestations of RA in CMCH

INCLUSION CRITERIA:

The cases fulfilling the American College of Rheumatism (ACR) and the EULAR criteria for rheumatoid arthritis.

EXCLUSION CRITERIA:

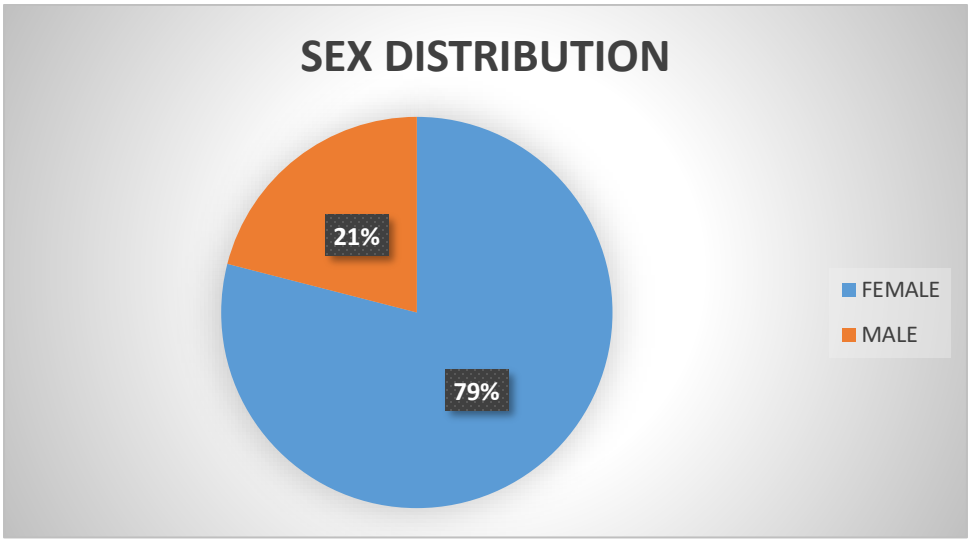
1) Patients presenting with polyarthritis but not satisfying the ACR and EULAR criteria.
2) Patients with other systemic illnesses
3) Patients with other causes of polyarthritis

RESULTS:

TABLE:3 SEX DISTRIBUTION

SEX	NO OF PATIENTS	PERCENTAGE
FEMALE	79	79%
MALE	21	21%

CHART:1



Out of 100 patients with RA,79% were females and 21% were males

TABLE 4:AGE DISTRIBUTION:

AGE IN YEARS	NO OF PATIENTS	PERCENTAGE
< 30	14	14%
31-45	37	37%
46-60	39	39%
> 60	10	10%

CHART 2:

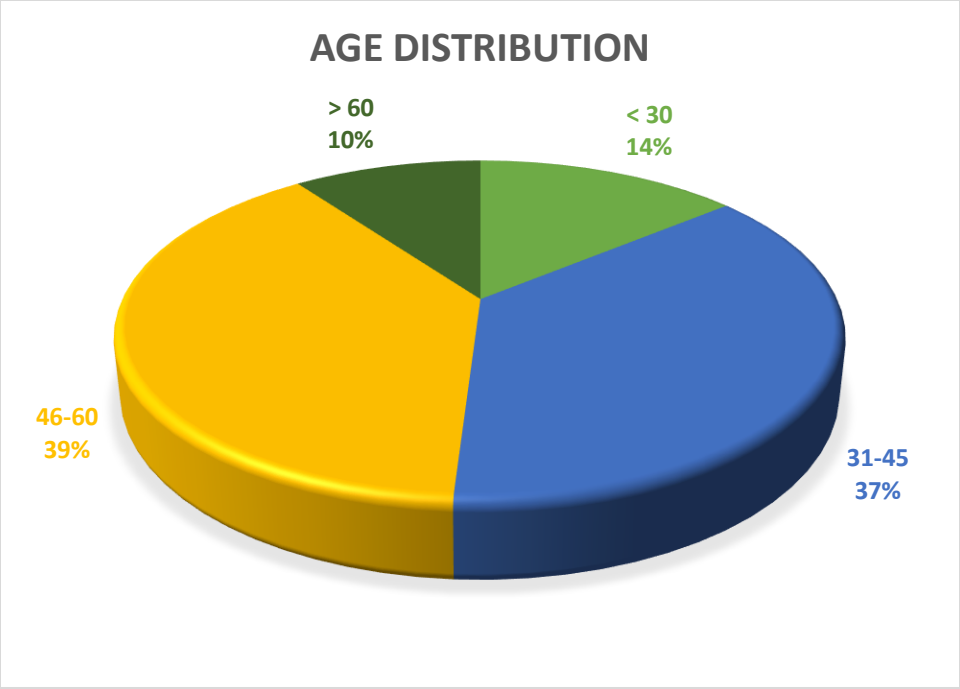


TABLE -5: RA FACTOR

RA FACTOR	NO OF PATIENTS	PERCENTAGE
POSITIVE	80	80%
NEGATIVE	20	20%

CHART 3:

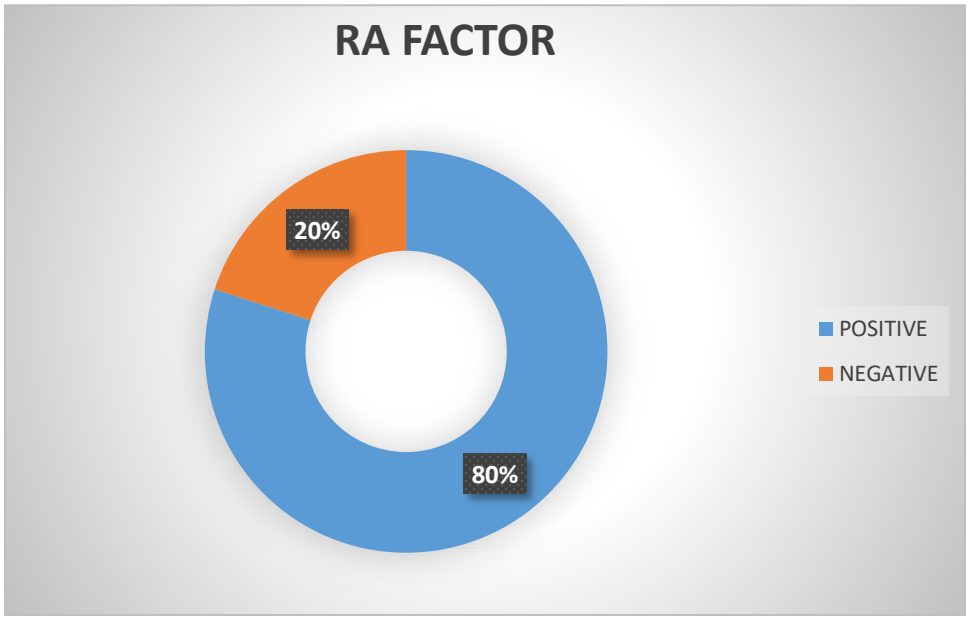


TABLE 6:DURATION OF DISEASE

DURATION OF DISEASE	NO OF PATIENTS	PERCENTAGE
< 5 YRS	34	34%
6-10 YRS	17	17%
11-20 YRS	37	37%
> 20 YRS	12	12%

In this study, those with duration of disease <5 years were 34%,

between 6 and 10 years were 17%,between 11 and 20 years were 37% and >20 years were 12%

CHART 4:DURATION OF DISEASE

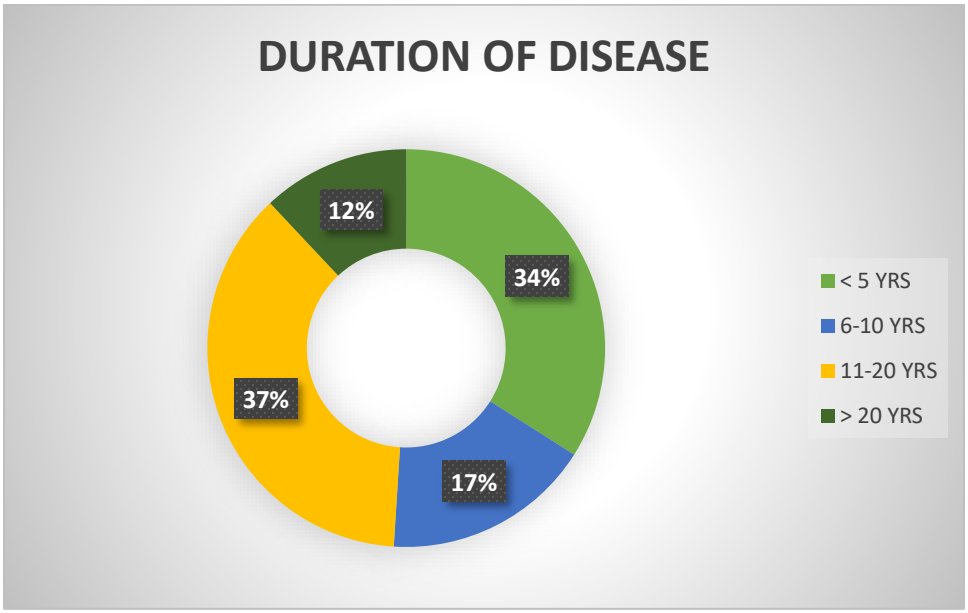


TABLE 7:EXTRA ARTICULAR MANIFESTATIONS

EXTRA ARTICULAR FEATURES	NO OF PATIENTS	PERCENTAGE
PRESENT	33	33%
ABSENT	67	67%

CHART: 5

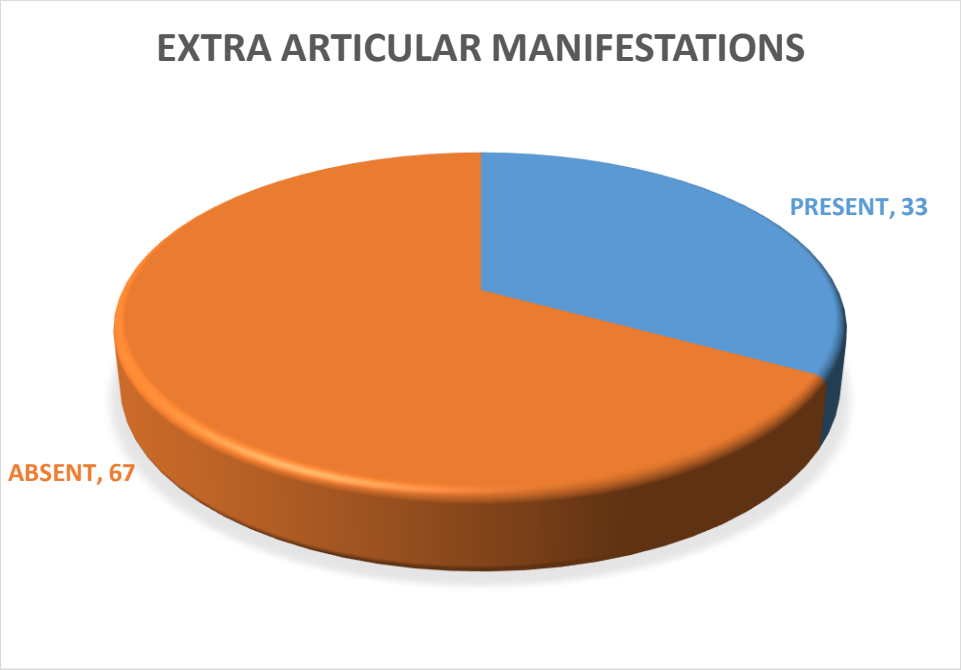


TABLE 8:SYSTEM WISE MANIFESTATIONS

EXTRA ARTICULAR MANIFESTATIONS – SYSTEMWISE		
SYSTEM	NO OF PATIENTS	PERCENTAGE
HEAMATOLOGICAL	14	42%
CARDIOLOGICAL	4	12%
DERMATOLOGICAL	8	24%
PULMONOLOGICAL	9	27%
OPHTHALMOLOGICAL	6	18%
OTHERS	3	10%
OVERLAP SYNDROMES	2	6%

CHART 6:

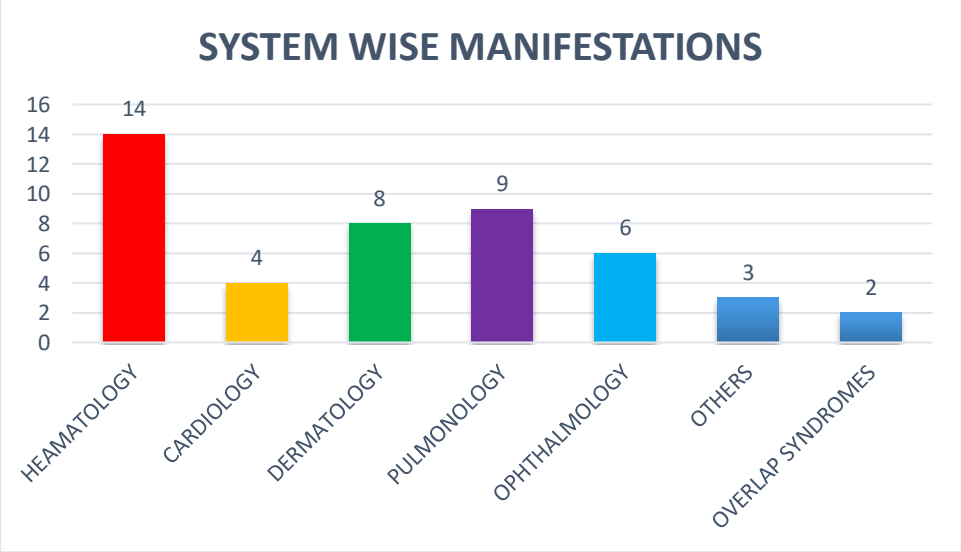


TABLE 9:EXTRA-ARTICULAR MANIFESTATIONS VS AGE

AGE	EXTRA ARTICULAR FEATURES	
	PRESENT	ABSENT
< 30	0	14
31-45	7	30
46-60	19	20
> 60	7	3
KRUSAL WALLIS TEST		
P VALUE - 0.001		
SIGNIFICANT		

CHART-7:

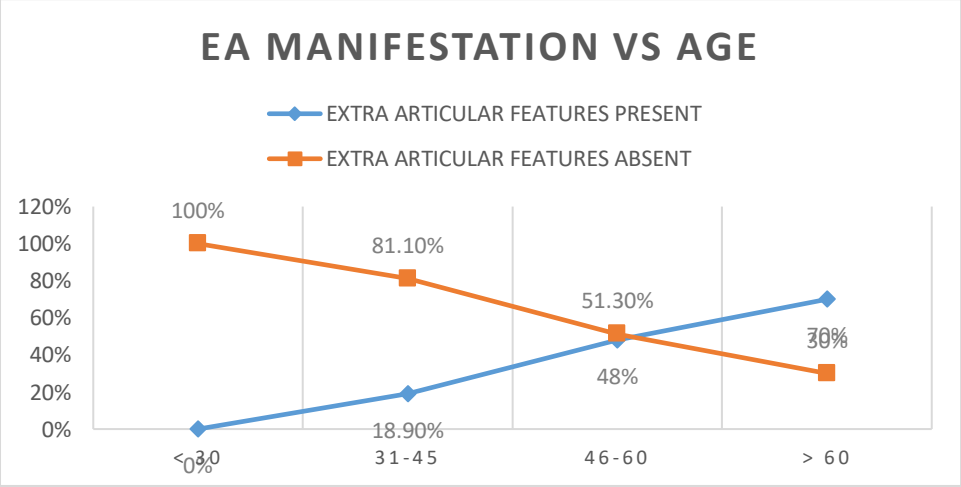


TABLE 10:EXTRA-ARTICULAR MANIFESTATIONS VS SEX

SEX	EXTRA ARTICULAR FEATURES	
	PRESENT	ABSENT
FEMALE	25	54
MALE	8	13
CHI SQUARE TEST		
P VALUE - 0.576		
NON SIGNIFICANT		

CHART 8: EXTRA-ARTICULAR MANIFESTATIONS VS SEX

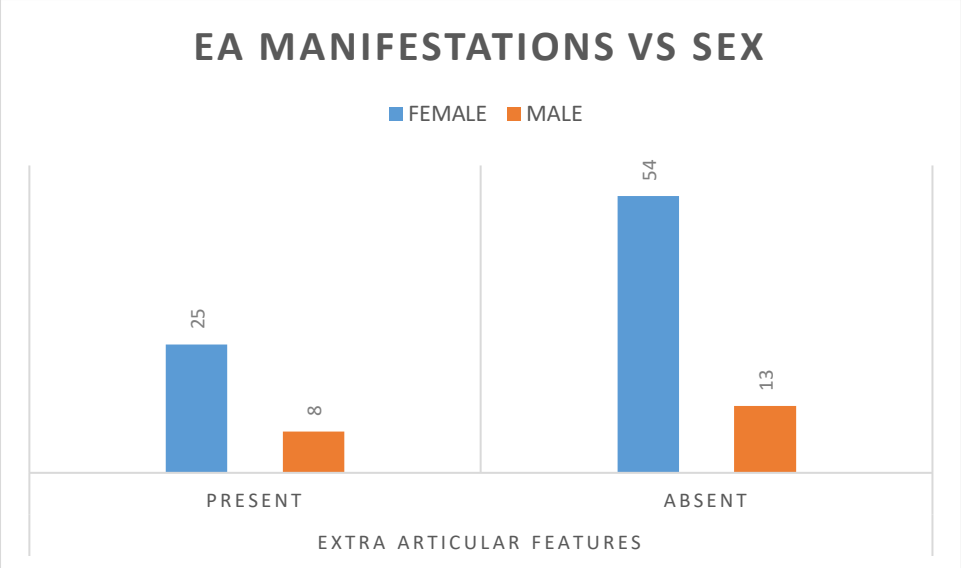


TABLE 11:EXTRA-ARTICULAR FEATURES VS RA FACTOR

RA FACTOR	EXTRA ARTICULAR FEATURES	
	PRESENT	ABSENT
POSITIVE	25	54
NEGATIVE	8	13
CHI SQUARE TEST		
P VALUE - 0.576		
NON SIGNIFICANT		

CHART 9 :

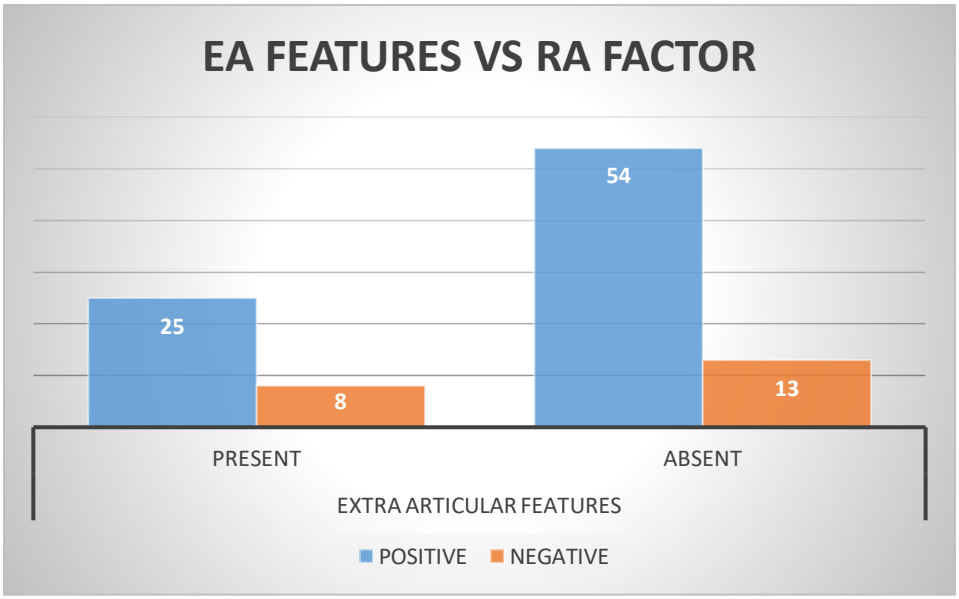


TABLE 12:EXTRA-ARTICULAR FEATURES VS DURATION OF DISEASE

DURATION OF DISEASE	EXTRA ARTICULAR FEATURES	
	PRESENT	ABSENT
< 5 YRS	4	30
6-10 YRS	7	10
11-20 YRS	12	25
> 20 YRS	10	2
KRUSKAL WALLIS TEST		
P VALUE - 0.001		
SIGNIFICANT		

CHART 10:

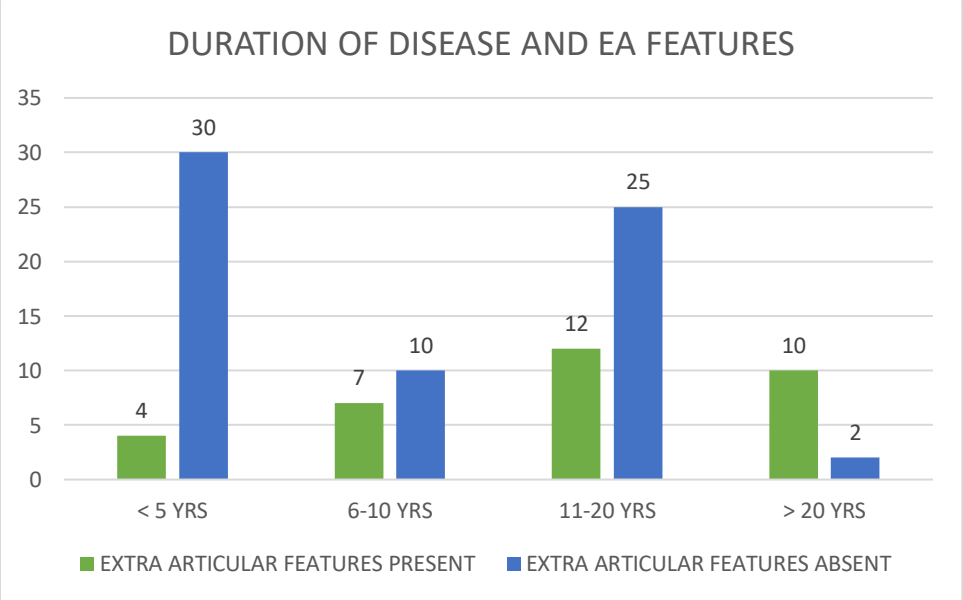


TABLE 13: HEMATOLOGICAL FEATURES

HAEMATOLOGY (N=14)	NO OF PATIENTS	PERCENTAGE
ANEAMIA OF CHRONIC DISEASE	6	42.85%
IRON DEFECIENCY ANEMIA	5	35.71%
MEGALOBLASTIC ANEMIA	1	7%
NEUTROPENIA	1	7%
EOSINOPHILIA	1	7%
THROMBOCYTOPENIA	1	7%
THROMBOCYTOSIS	1	7%

CHART 11:

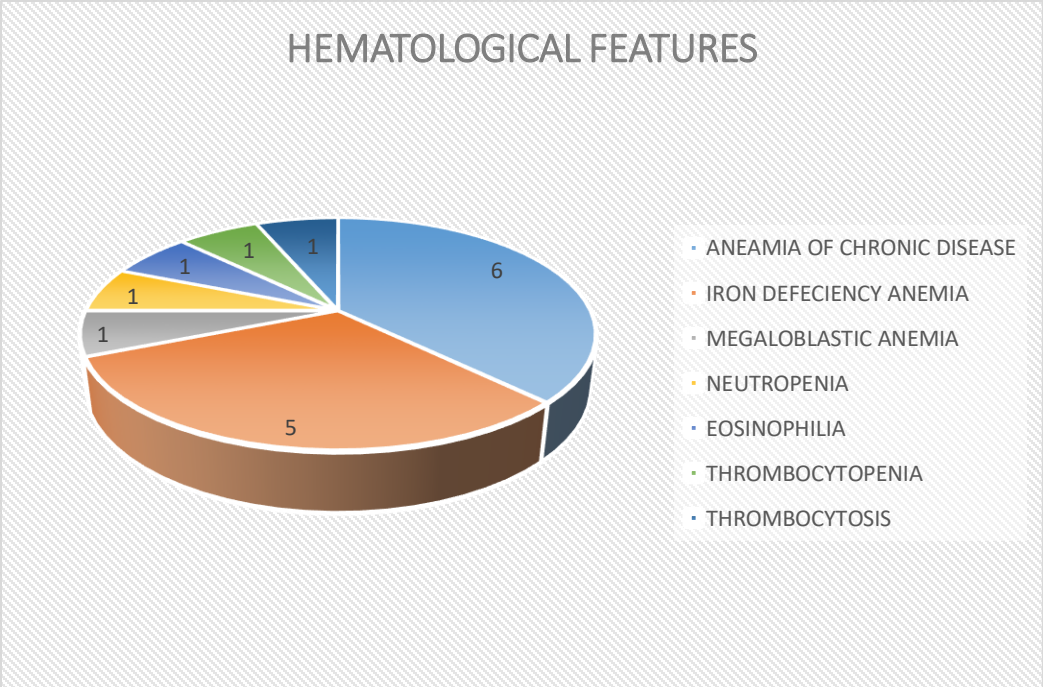


TABLE 14: HEMATOLOGICAL FEATURES VS AGE

AGE	HAEMATOLOGY FEATURES	
	PRESENT	ABSENT
< 30	0	14
31-45	1	36
46-60	9	30
> 60	4	6
KRUSAL WALLIS TEST		
P VALUE - 0.002		
SIGNIFICANT		

CHART 12:

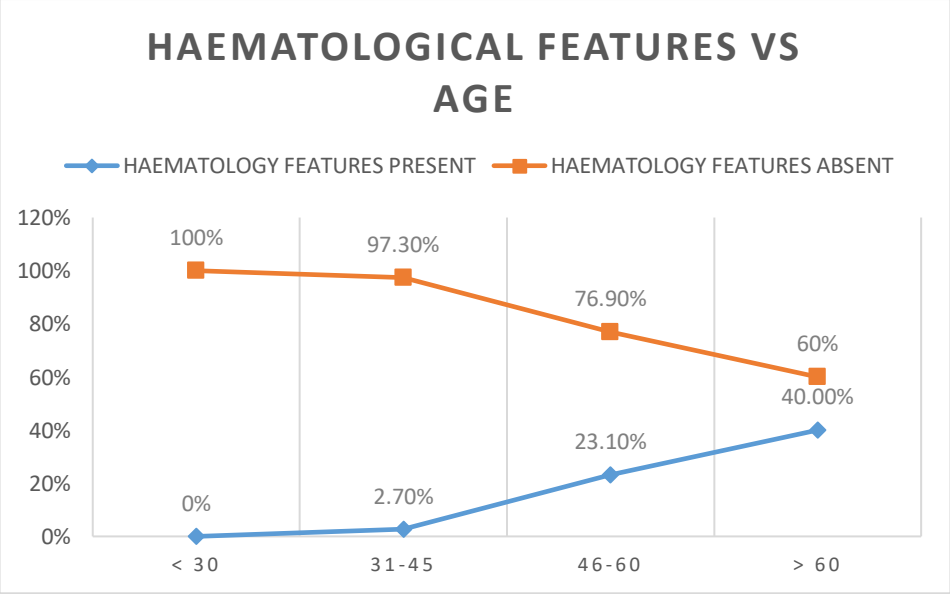


TABLE 15: HEMATOLOGICAL FEATURES VS SEX

SEX	HAEMATOLOGICAL FEATURES	
	PRESENT	ABSENT
FEMALE	12	67
MALE	2	19
CHI SQUARE TEST		
P VALUE - 0.506		
NON SIGNIFICANT		

CHART 13:

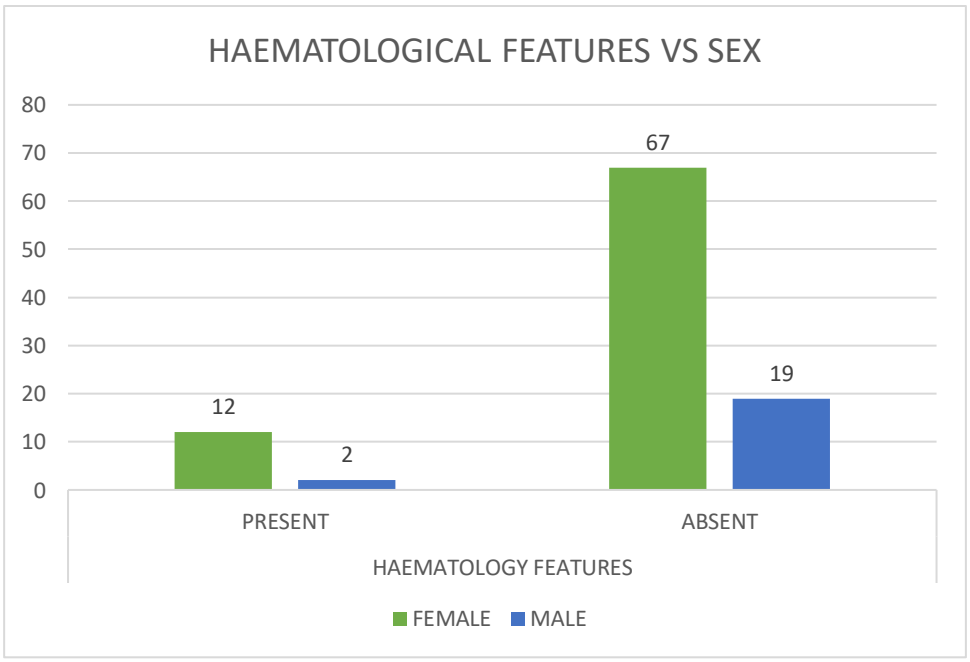


TABLE 16: HEMATOLOGICAL FEATURES VS RA FACTOR

RA FACTOR	HAEMATOLOGY FEATURES	
	PRESENT	ABSENT
POSITIVE	12	68
NEGATIVE	2	18
CHI SQUARE TEST		
P VALUE - 0.564		
NON SIGNIFICANT		

CHART 14:

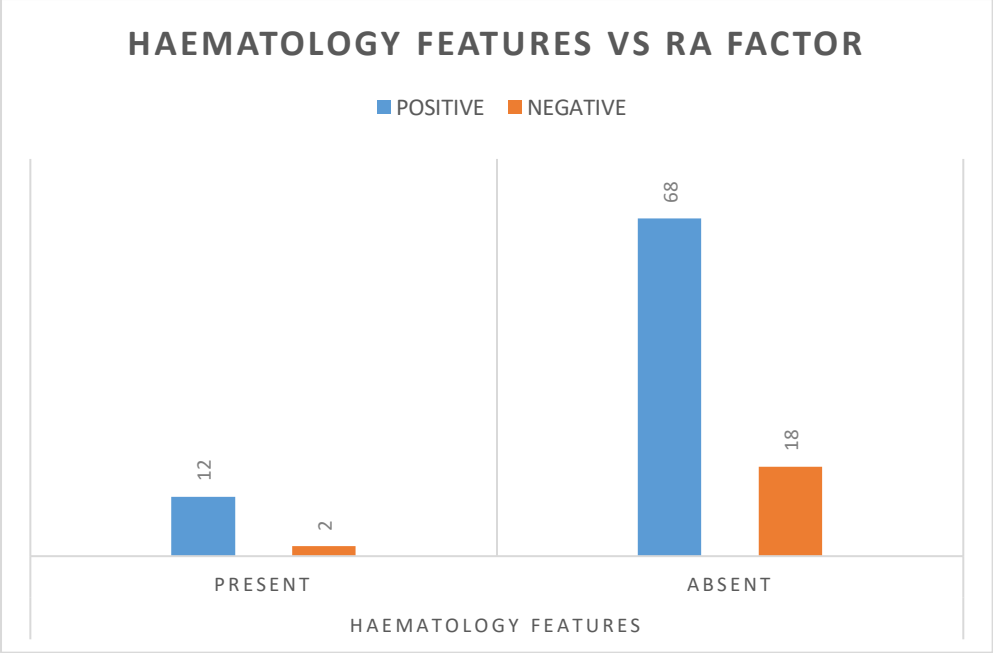


TABLE 17: HEMATOLOGICAL FEATURES VS DURATION OF DISEASE

DURATION OF DISEASE	HAEMATOLOGY FEATURES	
	PRESENT	ABSENT
< 5 YRS	0	34
6-10 YRS	2	15
11-20 YRS	3	34
> 20 YRS	9	3
KRUSKAL WALLIS TEST		
P VALUE - 0.001		
SIGNIFICANT		

CHART-15

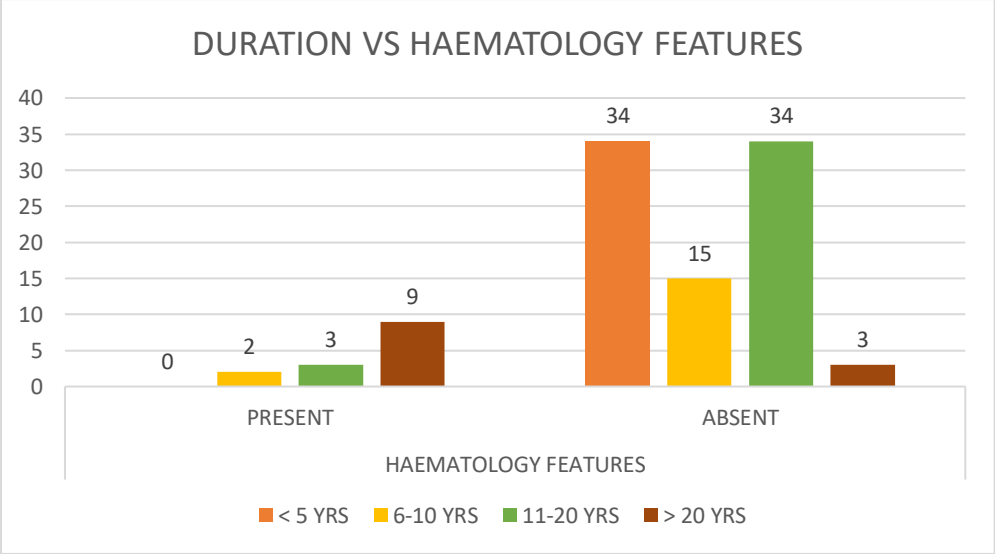


TABLE 18: CARDIAC MANIFESTATIONS

CARDIAC MANIFESTATION(N=4)	NO OF PATIENTS	PERCENTAGE
CARDIAC FAILURE	1	25.00%
PAH	2	50.00%
PERICARDIAL EFFUSION	1	25%

CHART 16:

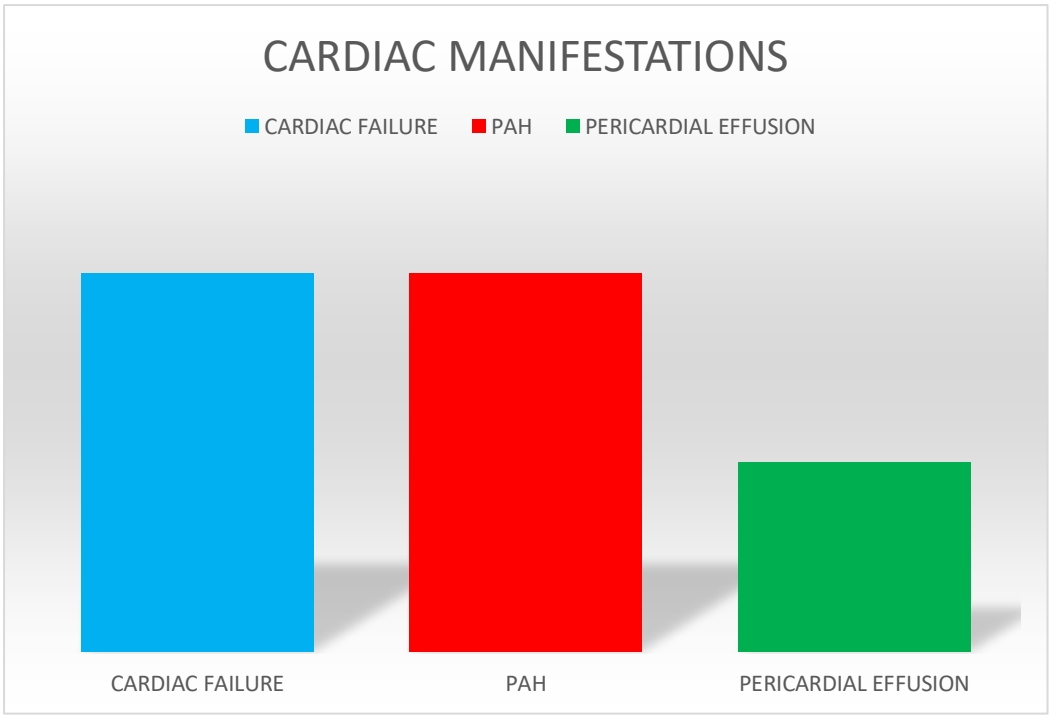


TABLE 19: CARDIAC MANIFESTATIONS VS AGE

AGE	CARDIAC MANIFESTATIONS	
	PRESENT	ABSENT
< 30	0	14
31-45	0	37
46-60	2	37
> 60	2	8
KRUSAL WALLIS TEST		
P VALUE - 0.03		
SIGNIFICANT		

CHART 17:

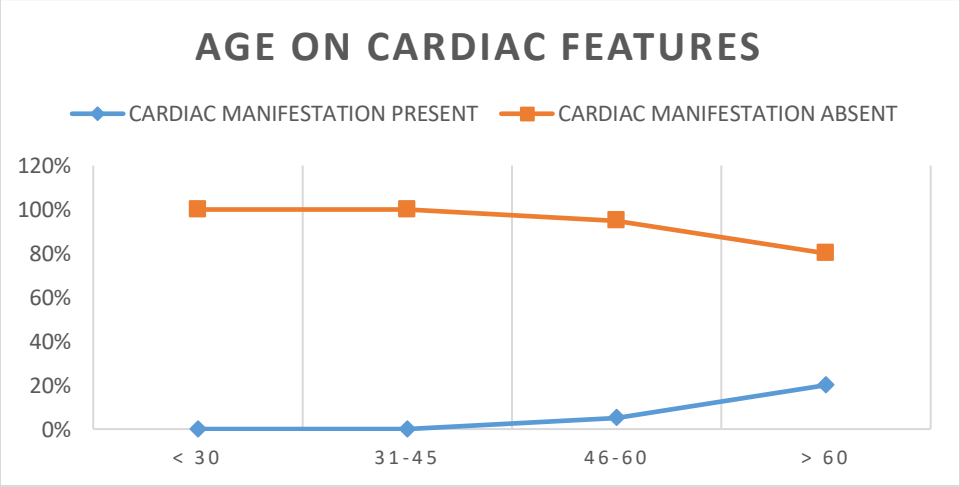


TABLE 20: CARDIAC MANIFESTATIONS VS SEX

SEX	CARDIAC MANIFESTATIONS	
	PRESENT	ABSENT
FEMALE	4	75
MALE	0	21
CHI SQUARE TEST		
P VALUE - 0.293		
NON SIGNIFICANT		

CHART 18

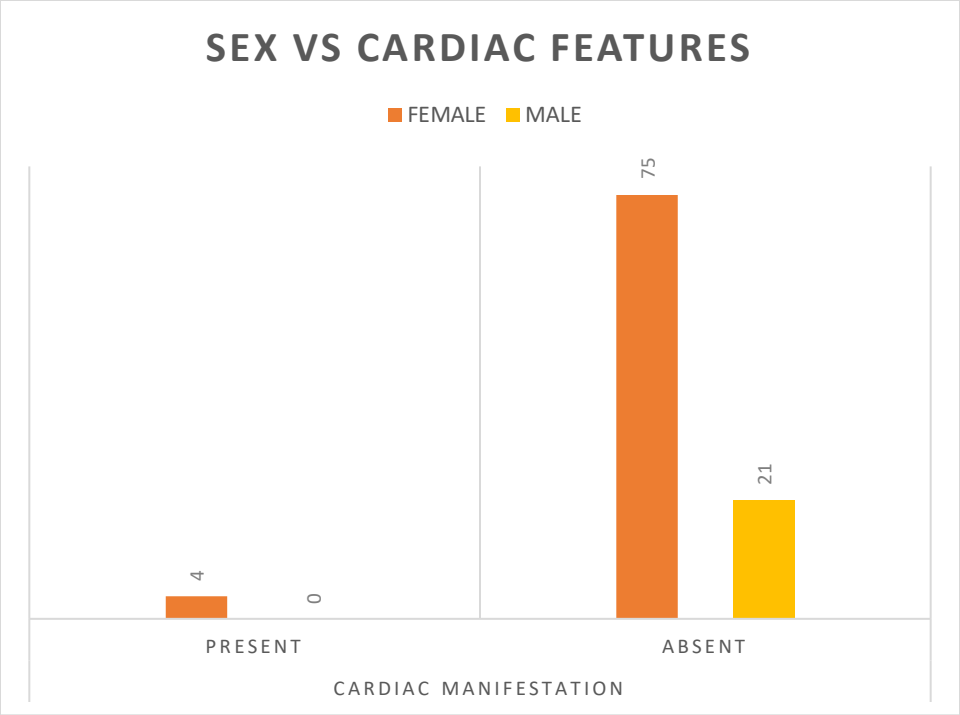


TABLE 21: CARDIAC MANIFESTATIONS VS RA FACTOR

RA FACTOR	CARDIAC MANIFESTATIONS	
	PRESENT	ABSENT
POSITIVE	4	76
NEGATIVE	0	20
CHI SQUARE TEST		
P VALUE - 0.367		
NON SIGNIFICANT		

CHART: 19

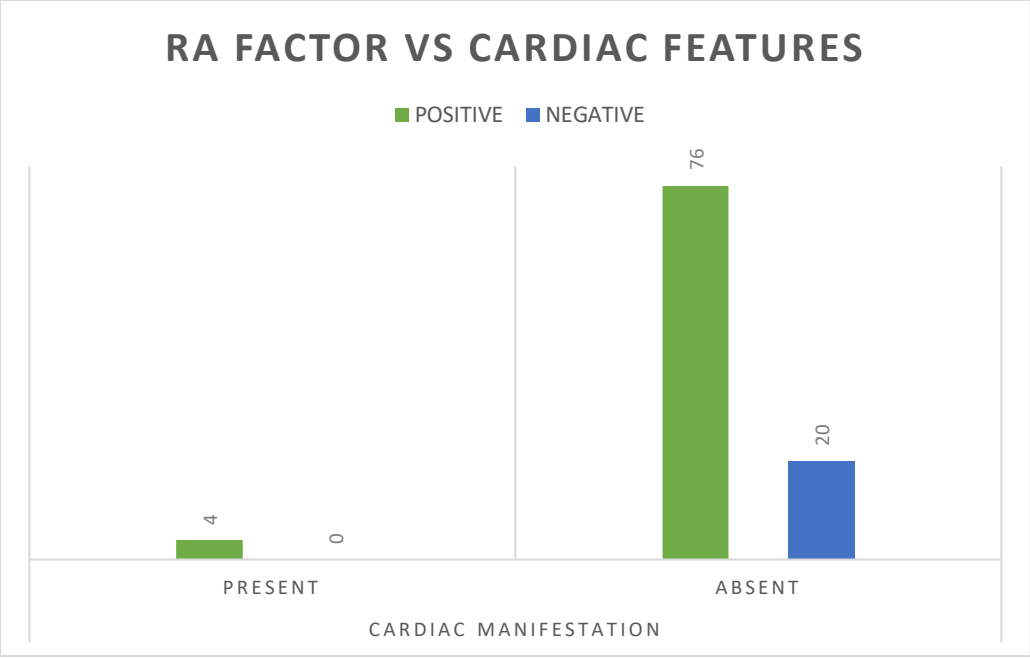


TABLE 22: CARDIAC MANIFESTATIONS VS DURATION OF DISEASE

DURATION OF DISEASE	CARDIAC MANIFESTATIONS	
	PRESENT	ABSENT
< 5 YRS	0	34
6-10 YRS	0	17
11-20 YRS	2	35
> 20 YRS	2	10
KRUSKAL WALLIS TEST		
P VALUE - 0.062		
NON SIGNIFICANT		

CHART 20:

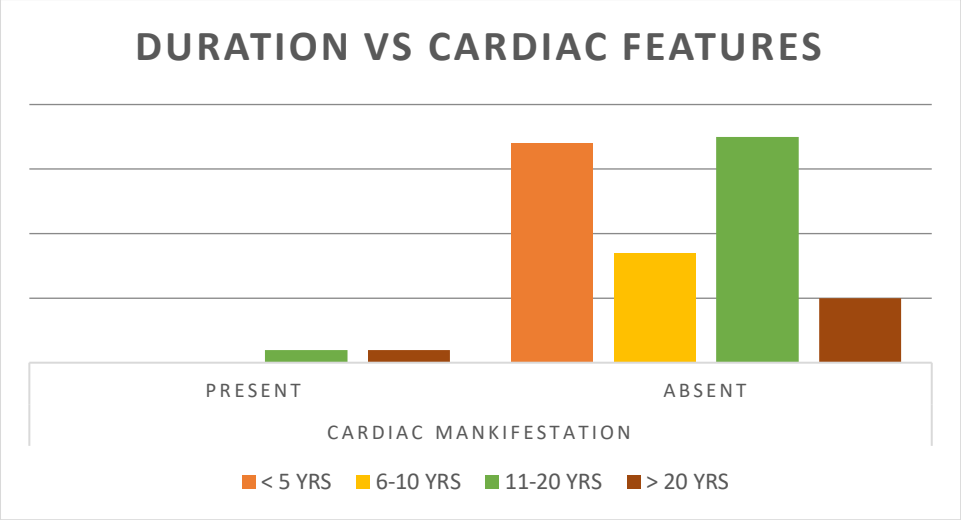


TABLE 23: DERMATOLOGICAL FEATURES

DERMATOLOGY (N=8)	NO OF PATIENTS	PERCENTAGE
RHEUMATOID NODULE	1	12.50%
BILATERAL LEG ULCERS	1	12.50%
SMALL VESSEL VASCULITIS	1	12.50%
RAYNAUDS PHENOMENON	1	12.50%
DIGITAL GANGRENE	1	12.50%
ATROPHIC SKIN WITH PURPURA	1	12.50%
PYODERMA GANGRENOSUM	1	12.50%

CHART 21:DERMATOLOGICAL MANIFESTATIONS

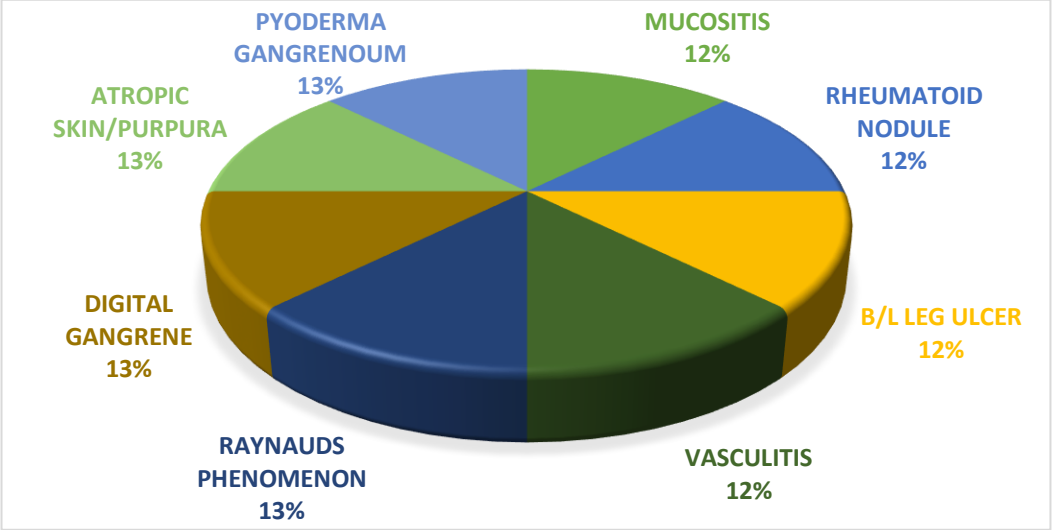


TABLE 24: SKIN CHANGES VS AGE

AGE	SKIN CHANGES	
	PRESENT	ABSENT
< 30	0	14
31-45	4	33
46-60	3	36
> 60	1	9
KRUSAL WALLIS TEST		
P VALUE - 0.643		
NON SIGNIFICANT		

CHART 22:

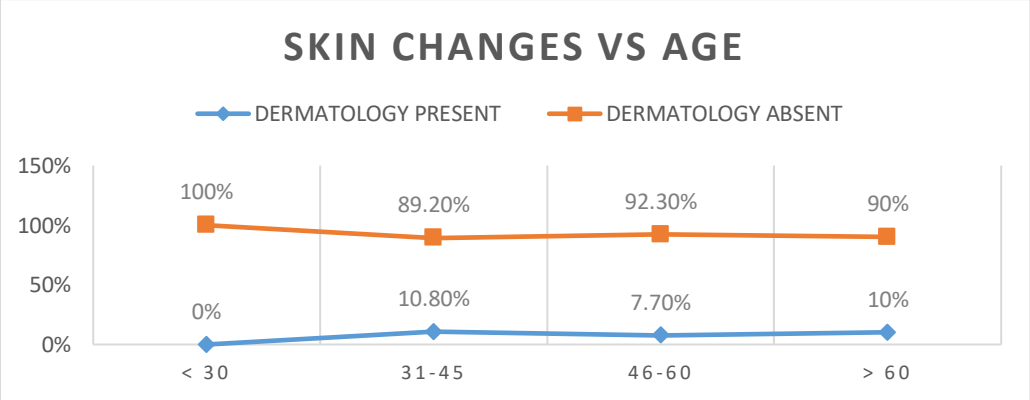


TABLE 25: SKIN CHANGES VS SEX

SEX	SKIN CHANGES	
	PRESENT	ABSENT
FEMALE	6	73
MALE	2	19
CHI SQUARE TEST		
P VALUE - 0.772		
NON SIGNIFICANT		

CHART 23:

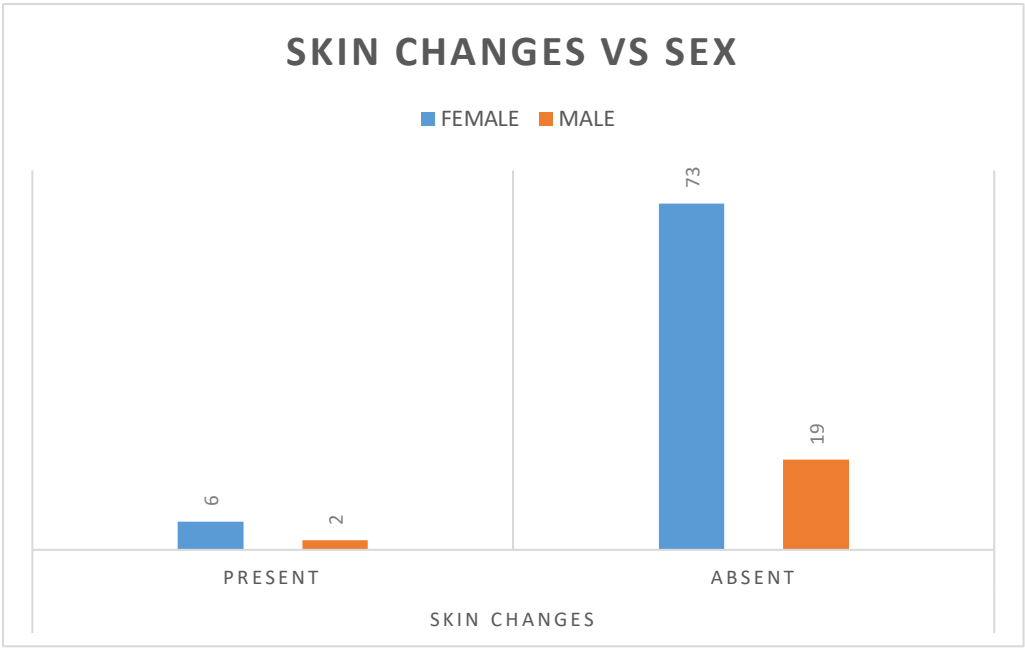


TABLE 26: SKIN CHANGES VS RA FACTOR

RA FACTOR	SKIN CHANGES	
	PRESENT	ABSENT
POSITIVE	7	73
NEGATIVE	1	19
CHI SQUARE TEST		
P VALUE - 0.580		
NON SIGNIFICANT		

CHART 24:

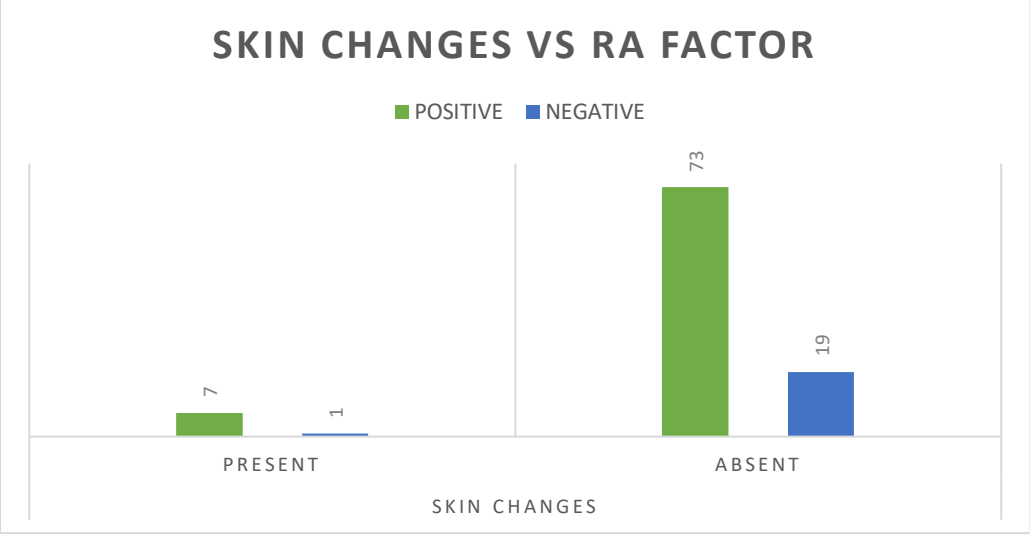


TABLE 27: SKIN CHANGES VS DURATION OF DISEASE

DURATION OF DISEASE	SKIN CHANGES	
	PRESENT	ABSENT
< 5 YRS	4	30
6-10 YRS	0	17
11-20 YRS	4	33
> 20 YRS	0	12
KRUSKAL WALLIS TEST		
P VALUE - 0.311		
NON SIGNIFICANT		

CHART 25:

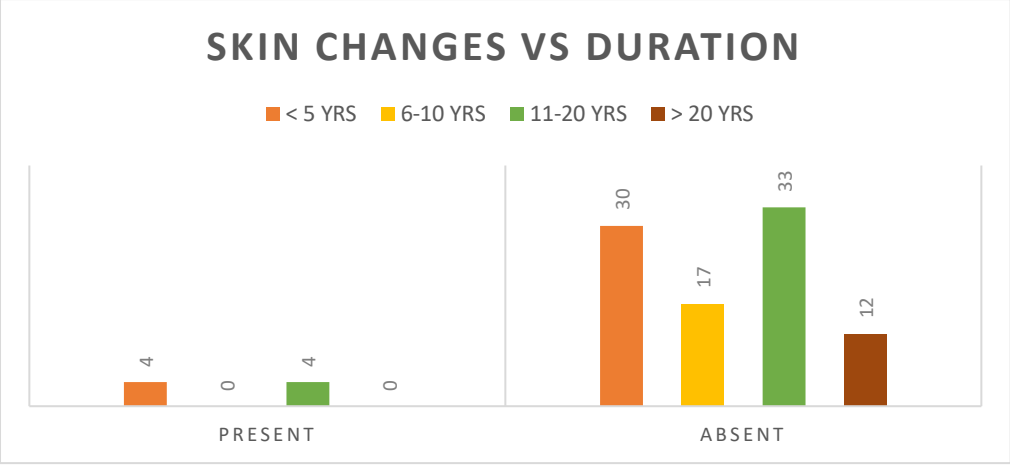


TABLE 28: PULMONARY MANIFESTATIONS

PULMONARY MANIFESTATIONS (N = 9)	NO OF PATIENTS	PERCENTAGE
INTERSTITIAL LUNG DISEASE	3	33.33%
RECURENT INFECTIONS	3	33.33%
PLEURAL EFFUSION	1	11%
PULMONARY FIBROSIS	1	11%
RESPIRATORY FAILURE	1	11%
EOSINOPHILIC PNEUMONIA	1	11%

CHART 26:

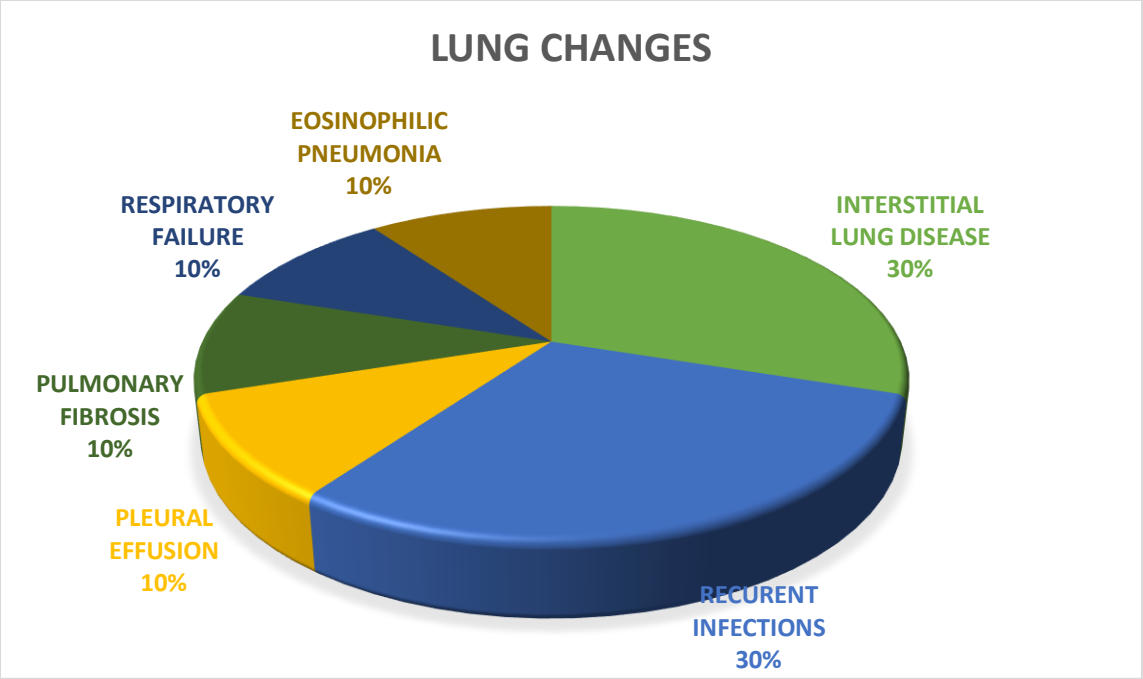


TABLE 29: PULMONARY MANIFESTATIONS VS AGE

AGE	PULMONARY MANIFESTATIONS	
	PRESENT	ABSENT
< 30	0	14
31-45	1	36
46-60	5	34
> 60	3	7
KRUSAL WALLIS TEST		
P VALUE - 0.026		
SIGNIFICANT		

CHART 27:

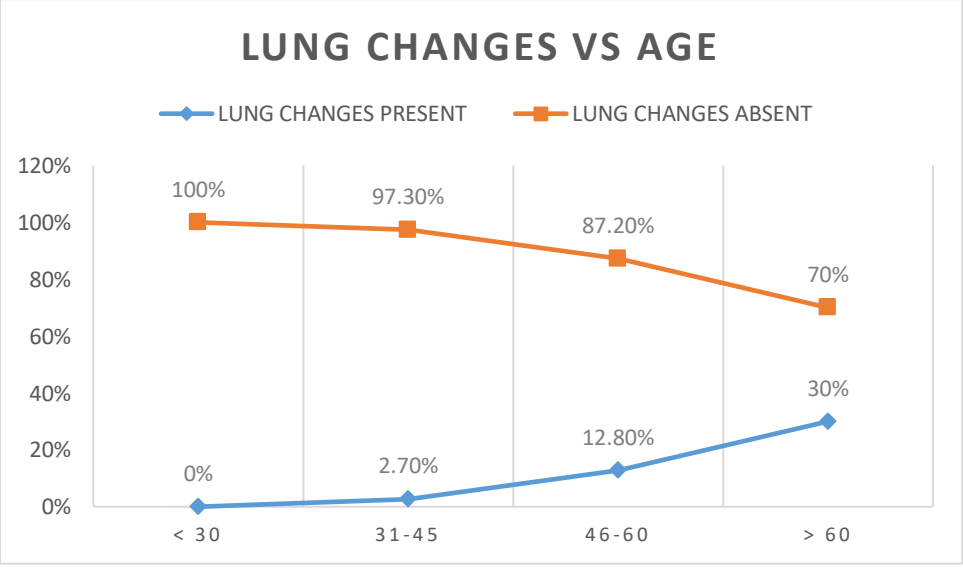


TABLE 30: PULMONARY MANIFESTATIONS VS SEX

SEX	PULMONARY MANIFESTATIONS	
	PRESENT	ABSENT
FEMALE	7	72
MALE	2	19
CHI SQUARE TEST		
P VALUE - 0.925		
NON SIGNIFICANT		

CHART 28:

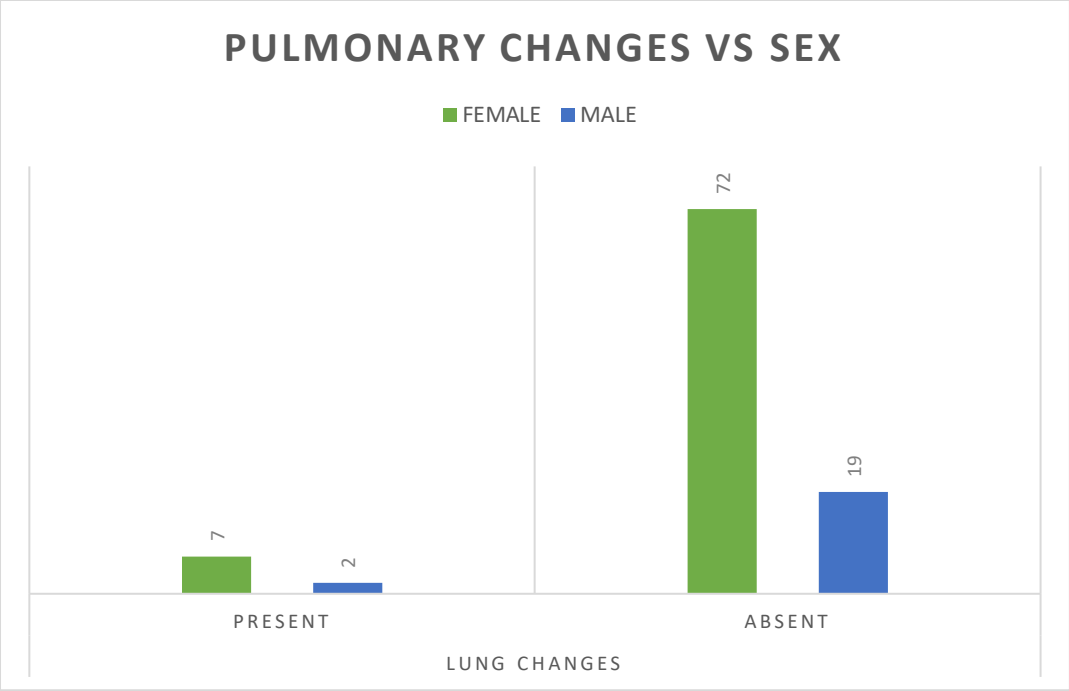


TABLE 31: PULMONARY MANIFESTATIONS VS RA FACTOR

RA FACTOR	PULMONARY MANIFESTATIONS	
	PRESENT	ABSENT
POSITIVE	6	74
NEGATIVE	3	17
CHI SQUARE TEST		
P VALUE - 0.295		
NON SIGNIFICANT		

TABLE 29:

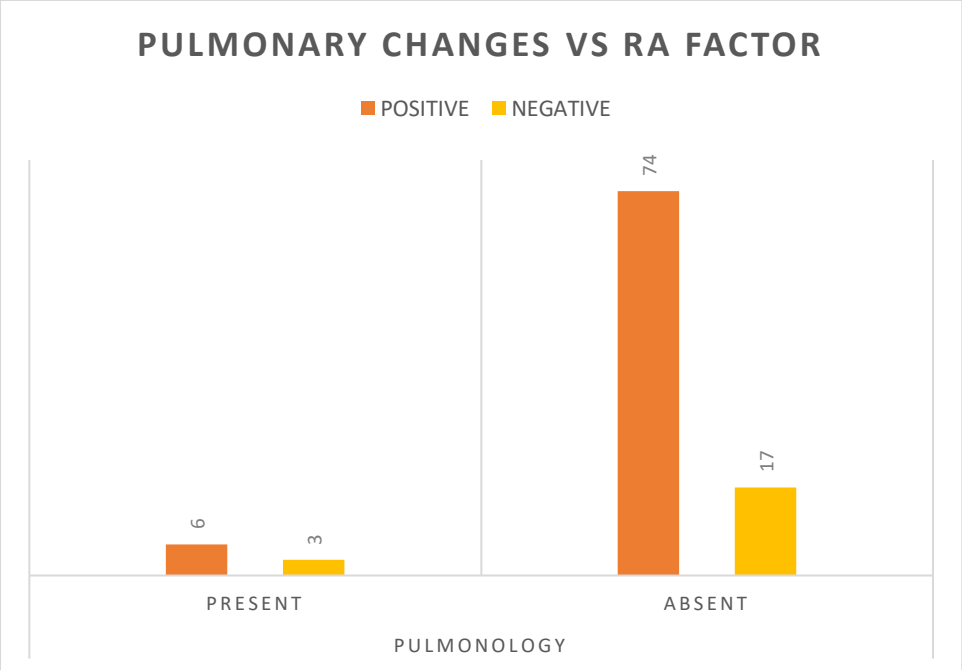


TABLE 32: PULMONARY MANIFESTATIONS VS DURATION OF DISEASE

DURATION OF DISEASE	PULMONARY MANIFESTATIONS	
	PRESENT	ABSENT
< 5 YRS	0	34
6-10 YRS	3	14
11-20 YRS	2	35
> 20 YRS	4	8
KRUSKAL WALLIS TEST		
P VALUE - 0.003		
SIGNIFICANT		

CHART 30:

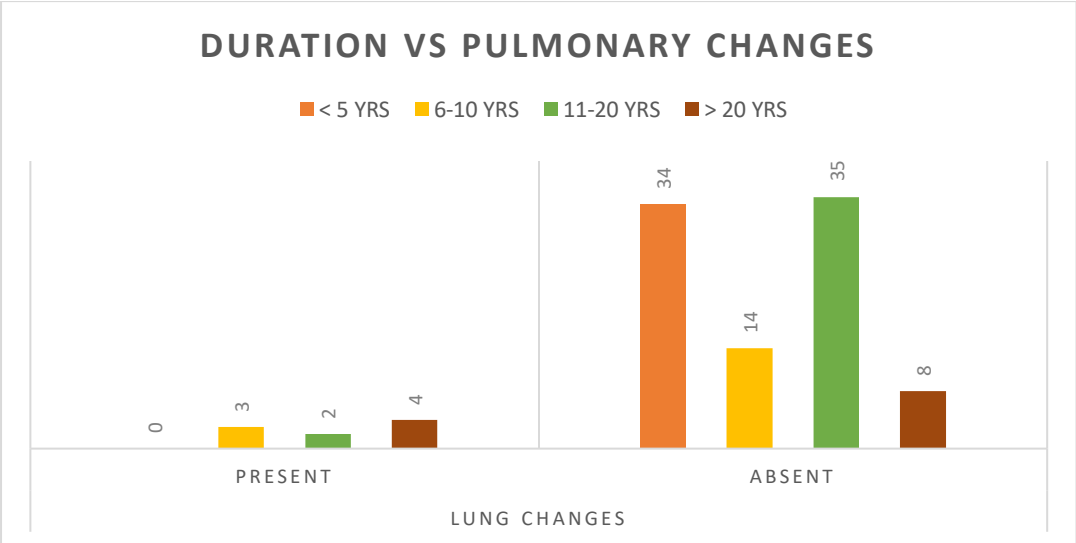


TABLE 33: OPHTHALMOLOGICAL CHANGES

EYE CHANGES	NO OF PATIENTS	PERCENTAGE
DRY EYE	5	83.00%
EPISCLERITIS	1	17.00%

CHART 31:

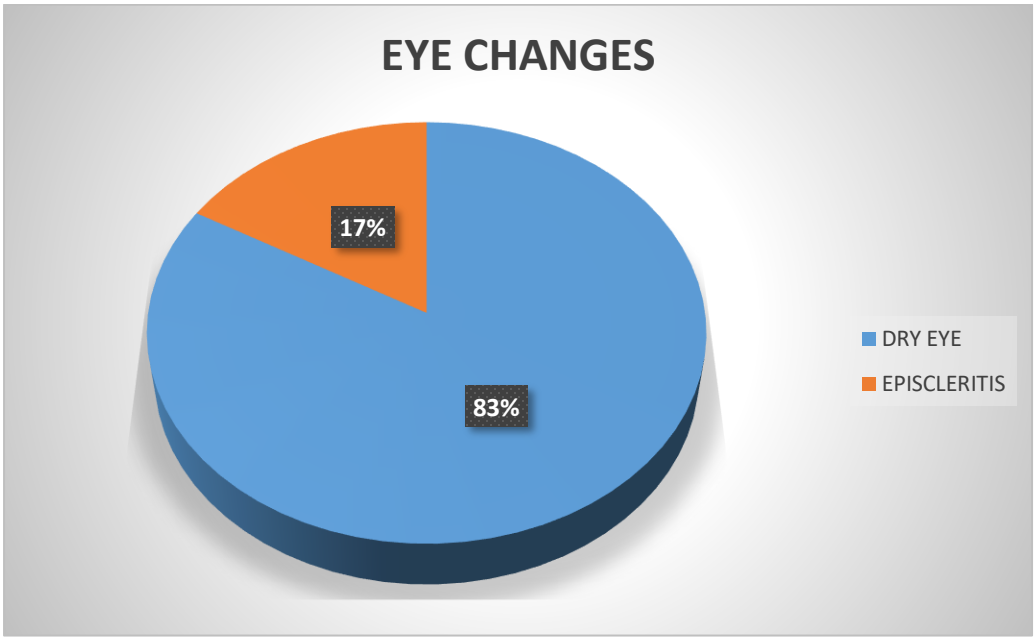


TABLE 34: EYE CHANGES VS AGE

AGE	EYE CHANGES	
	PRESENT	ABSENT
< 30	0	14
31-45	1	36
46-60	3	36
> 60	2	8
KRUSAL WALLIS TEST		
P VALUE - 0.152		
NON SIGNIFICANT		

CHART 32:

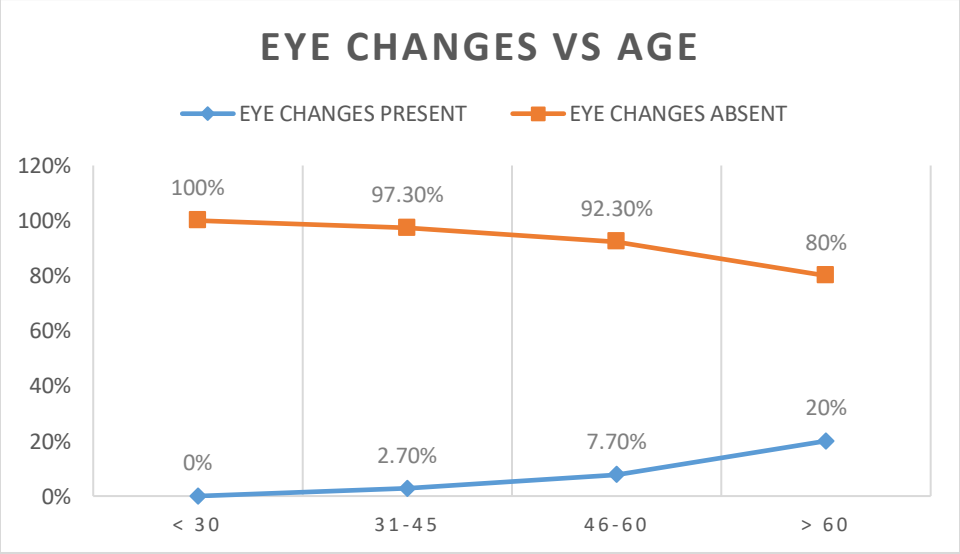


TABLE 35: EYE CHANGES VS SEX

SEX	EYE CHANGES	
	PRESENT	ABSENT
FEMALE	4	75
MALE	2	19
CHI SQUARE TEST		
P VALUE - 0.444		
NON SIGNIFICANT		

CHART 33:

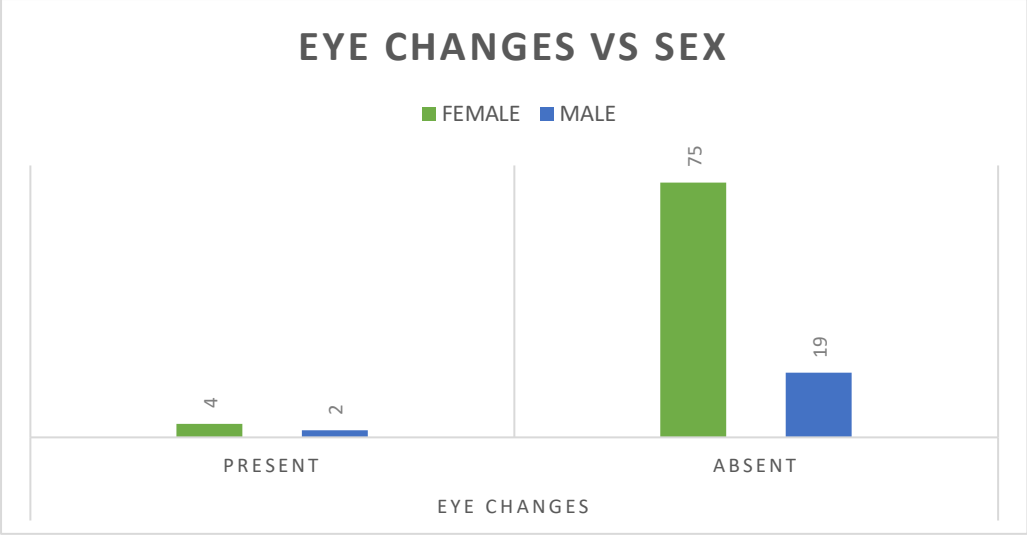


TABLE 36: EYE CHANGES VS RA FACTOR

RA FACTOR	EYE CHANGES	
	PRESENT	ABSENT
POSITIVE	5	75
NEGATIVE	1	19
CHI SQUARE TEST		
P VALUE - 0.833		
NON SIGNIFICANT		

CHART 34:

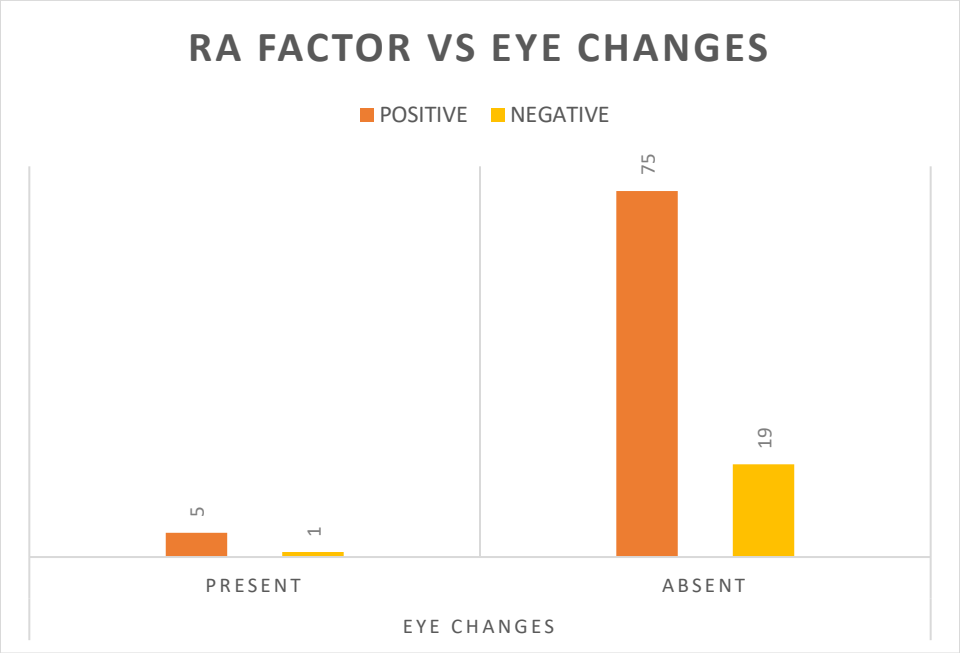


TABLE 37: EYE CHANGES VS DURATION OF DISEASE

DURATION OF DISEASE	OPHTHALMOLOGICAL MANIFESTATIONS	
	PRESENT	ABSENT
< 5 YRS	1	33
6-10 YRS	0	17
11-20 YRS	3	34
> 20 YRS	2	10
KRUSKAL WALLIS TEST		
P VALUE - 0.225		
SIGNIFICANT		

CHART : 35

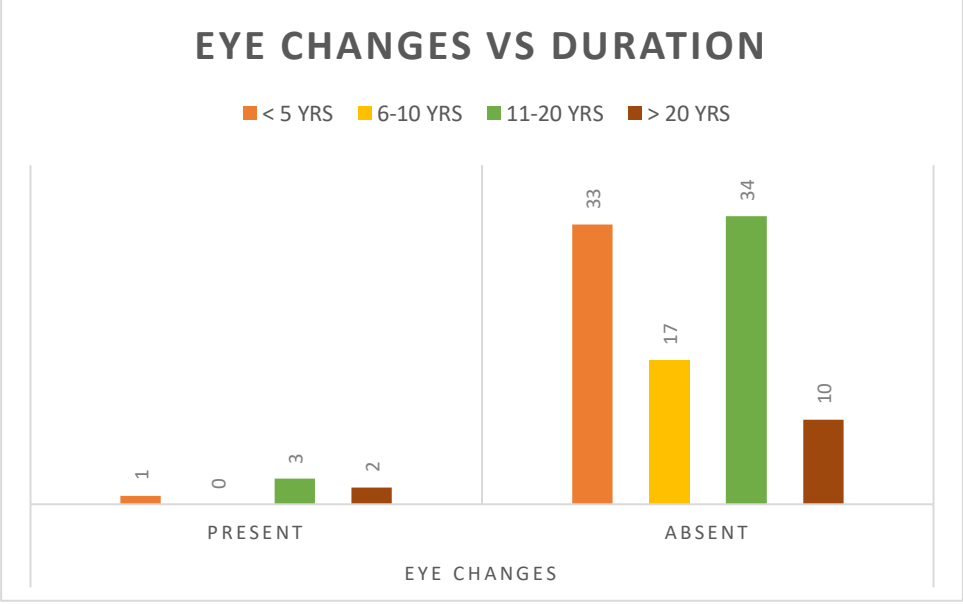


TABLE 38: OTHER MANIFESTATIONS

OTHERS	NO OF PATIENTS	PERCENTAGE
DISTAL POLYNEUOPATHY	1	33.33%
MONONEURITIS MULTIPLEX	1	33.33%
DRUG INDUCED UGI BLEED	1	33%

CHART 36:

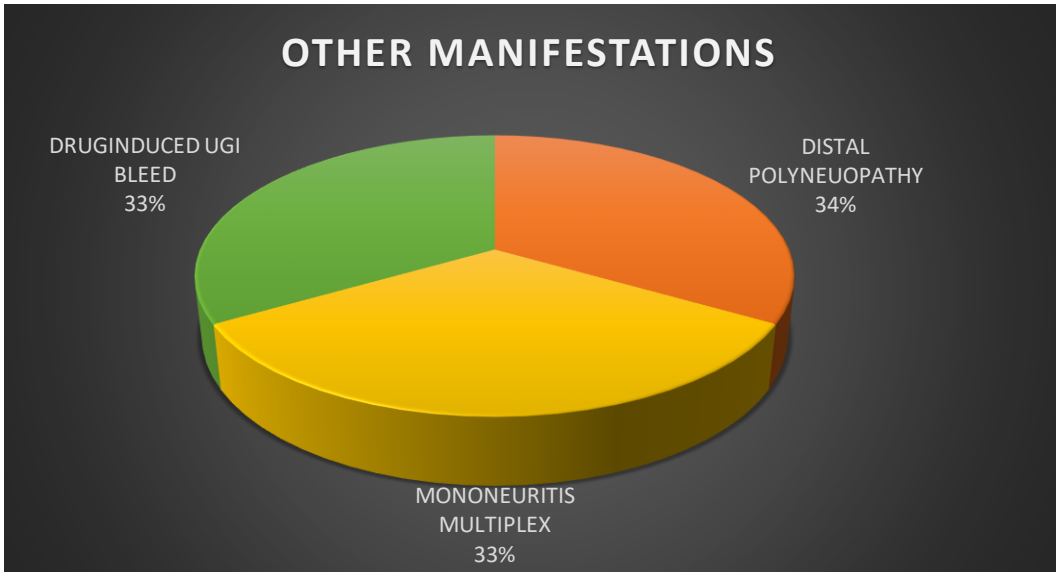


TABLE 39: OTHER FEATURES VS AGE

AGE	OTHER FEATURES	
	PRESENT	ABSENT
< 30	0	14
31-45	0	37
46-60	3	36
> 60	0	10
KRUSAL WALLIS TEST		
P VALUE - 0.124		
NON SIGNIFICANT		

CHART 37

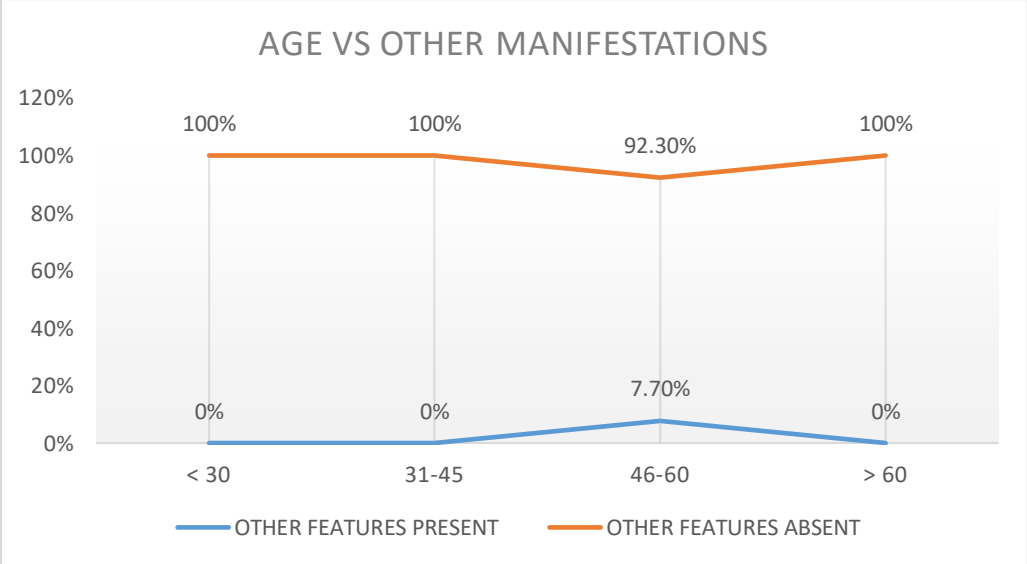


TABLE 40: OTHER FEATURES VS SEX

SEX	OTHER FEATURES	
	PRESENT	ABSENT
FEMALE	2	77
MALE	1	20
CHI SQUARE TEST		
P VALUE - 0.594		
NON SIGNIFICANT		

CHART 38:

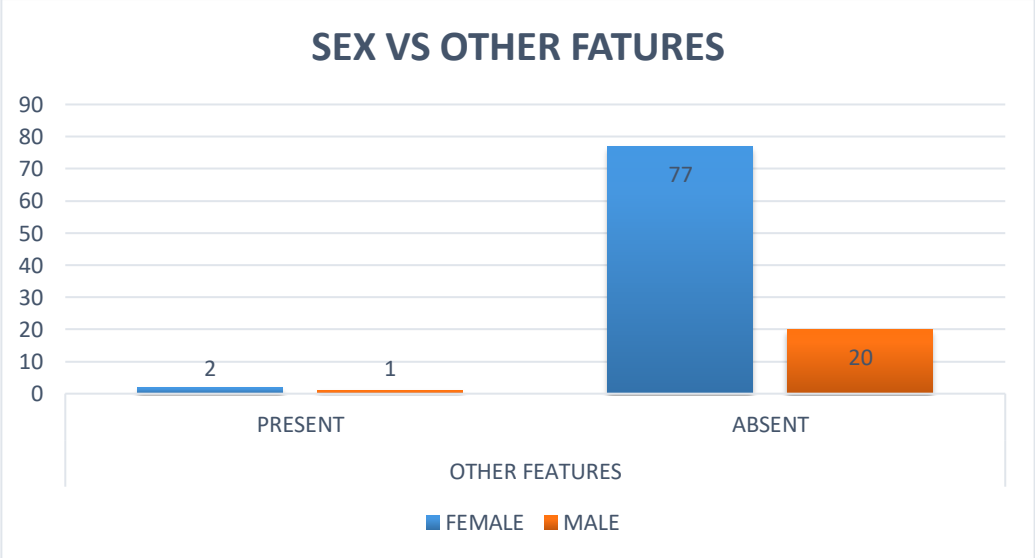


TABLE 41: OTHER FEATURES VS RA FACTOR

RA FACTOR	OTHER FEATURES	
	PRESENT	ABSENT
POSITIVE	2	78
NEGATIVE	1	19
CHI SQUARE TEST		
P VALUE - 0.558		
NON SIGNIFICANT		

CHART 39:

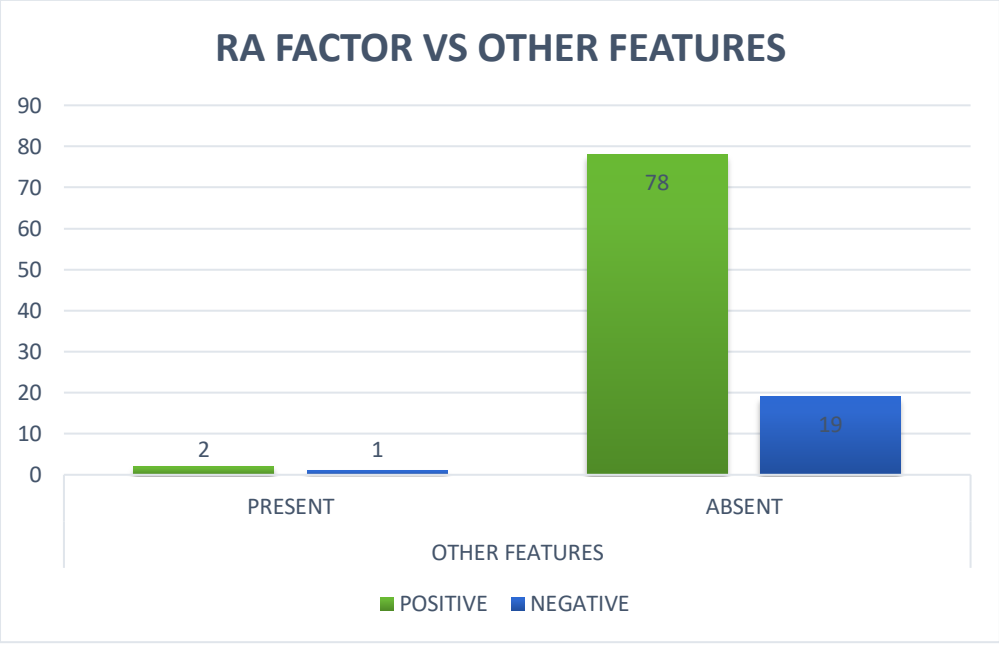


TABLE 42: OTHER FEATURES VS DURATION OF DISEASE

DURATION OF DISEASE	OTHER FEATURES	
	PRESENT	ABSENT
< 5 YRS	0	34
6-10 YRS	0	17
11-20 YRS	2	35
> 20 YRS	1	11
KRUSKAL WALLIS TEST		
P VALUE - 0.323		
NON SIGNIFICANT		

CHART 40:

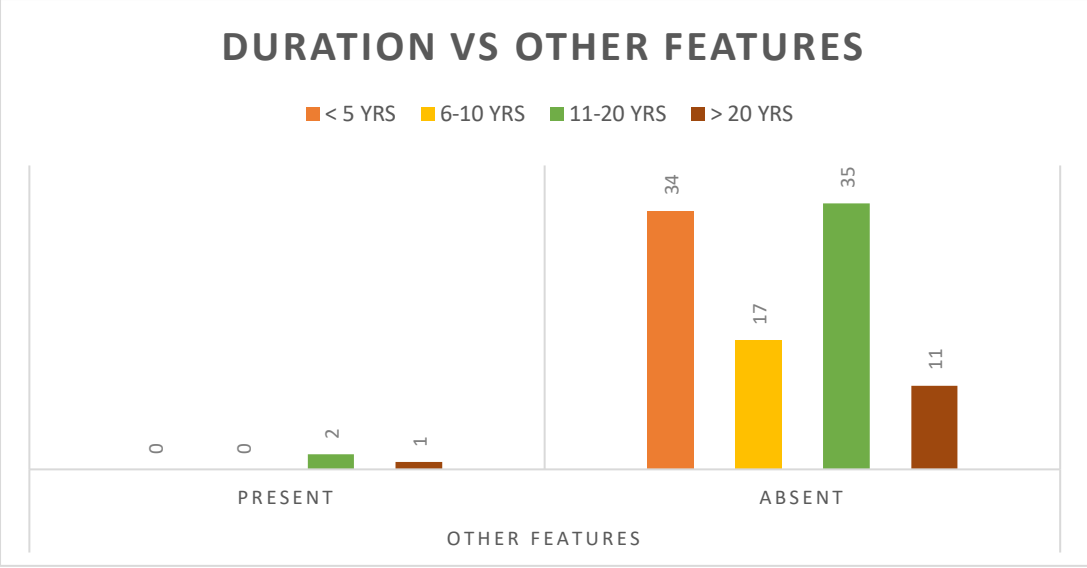


TABLE 43: OVERLAP SYNDROME

OVERLAP SYNDROME	NO OF PATIENTS	AGE	SEX
SLE OVERLAP	1	40	FEMALE
SCLERODERMA OVERLAP	1	47	FEMALE

OVERLAP SYNDROME	DURATION OF DISEASE	RA FACTOR
SLE OVERLAP	6-10 YRS	POSITIVE
SCLERODERMA OVERLAP	6-10 YRS	NEGATIVE

DISCUSSION

This study was conducted in Coimbatore medical college hospital from June 2017 to June 2018. A total of 100 cases were studied. The clinical and diagnostic findings of this study are compared with our studies in literature

SEX DISTRIBUTION:

The ratio of male to female in current study is 1:2.9.

In the study done by Turesson C et al, the ratio of male to female patients was 1:2.71.The sex ratio in this study is comparable to the same in the current study.

AGE DISTRIBUTION:

The age incidence in the current study is 53.66 years

In the study done by Maioneet al.,the mean age of the study group was 46.4 years.the age incidence in this study is lower than the mean age in the current study.

RHEUMATOID FACTOR:

Pai et al.,Jonssonet al.,Sahatciu-Mekaet al.,Turesson et al., all have found high percentage of their cases to be rheumatoid factor positive. All have found rheumatoid factor positivity together with higher percentage of extra-articular manifestation. In this study 80% of RA patients were sero-positive for RA factor and 20% were seronegative.this is comparable to the above quoted study.

DURATION OF DISEASE:

The mean duration of disease in the present study is 11-20years

In the study done by Turesson et al., the mean duration of disease was found to be 11.8years.this is comparable to the present study.

EXTRA-ARTICULAR MANIFESTATIONS: in the study out of 100 patients ,33% of RA patient had extra-articular manifestations.

SYSTEM	NO.OF PATIENTS	PERCENTAGE %
HAEMETOLOGY	14	42
CARDIOLOGY	4	12
DERMATOLOGY	8	24
PULMONOLOGY	9	27
OPHTHALMOLOGY	6	18
OTHERS	3	10
OVERLAPSYNDROMES	2	6

HEMATOLOGICAL MANIFESTATIONS:

In the present study predominant extra-articular manifestation is hematological. The most common is anaemia of chronic disease and is present in 42.85%

In the study done by Sahatciu-Meka et al.,anaemia was the predominant manifestation with 97.8%of the patients having anaemia. this is higher comparable to the present study. various haematological manifestations observed in these patients were anaemia of chronic disease-42.85%, iron deficiency anaemia-35.71%,megaloblastic anaemia-7%,neutropenia-7%,eosinophilia-7%,thrombocytopenia-7%, thrombocytosis -7%

CARDIAC MANIFESTATIONS:

In the present study, cardiac manifestations constitute 12%.the various manifestations seen are cardiac failure ,pulmonary artery hypertension and pericardial effusion

In the study done by Maione et al. ,cardiac manifestations were seen in 43% of the patients which is higher compared to the current study

OCULAR MANIFESTATIONS:

In the present study ,ocular manifestations are found in 18%. ophthalmological manifestations observed in this study were dry eyes(83%) and episcleritis(17%)

In the study done by Fleming A et al. , episcleritis was observed in 9%of the cases scleritis was observed in 4% of cases .In the current study shows higher incidence of episcleritis than this study

DERMATOLOGICAL MANIFESTATIONS :

It was present in 8 patients out of 33 which is 24%.and various manifestations include methotrexate induced mucositis, rheumatoid nodule, bilateral leg ulcers, small vessel vascuitis, raynaud phenomenon, digital gangrene,atrophic skin with purpura and pyoderma gangrenosum.

In the study done by Sharma et al, vasculitis was present in 2%. In our study vasculitis was present in 12.5% which was higher than the study quoted.

In our study rheumatoid nodule was found in 12.5%.in the study done by Sahatciu-Meka et al., rheumatoid nodules were seen in 12% of the cases. this is comparable to our study.

In our study raynaud phenomenon was present in 12.5%.in the study done by M.Calguineri et al raynauds was present in 3% of patients which is lesser comparable to current study.

In the current study purpura was present in 12.5%. In the study done by Sahatciu-Meka et al.,purpura was observed in 12% of the cases. This is comparable to current study

PULMONARY MANIFESTATIONS:

In the current study pulmonary manifestation was present in 27%.In the study done by Sandipan Banik et al pulmonary involvement occur in 33%.this is comparable to the current study. In this study pulmonology manifestations were present in 9 patients out of 33 and it is the second most common extra-articular manifestations of RA.3 had interstitial lung disease 3 had recurrent infections. 1 had pleural effusion 1 had pulmonary fibrosis 1 had respiratory failure 1 had eosinophilic pneumonia. Those with duration of illness more than 20yrs 4 had pulmonological manifestations .

PERIPHERAL NEUROPATHY

In the current study peripheral neuropathy was present in 6%.In the study done by Turesson et al peripheral neuropathy is seen in 2.1% of cases. This is lower compared to current study. The other manifestations observed in this study include distal poly-neuropathy which is present in 1patient and mononeuritis multiplex is present in 1 patient

OTHERS

Drug induced UGI bleed is present in 1 patient.

OVERLAP SYNDROMES

ANA was done for these patients and SLE overlap was found in 1 patient. She was 40yrs female with 6-10 yrs of disease with seropositivity of RF. Scleroderma overlap was present in 1 patient. She was 47yrs old female with 6-10yrs of disease with seronegative for RA factor

The overall presence of majority of extra-articular manifestation is lesser in the present study as compared to other studies. This could be attributed to the following reasons:

1. The incidence of extra-articular manifestations is much lower in Indian patients as evidenced by the Kaushal et al study

2. The duration of disease was much lower in this study as compared to other studies.

3. The number of cases in the present study is much lower compared to the other studies.

Conclusion

Extra-articular manifestations were found in 33 cases of rheumatoid arthritis and the highest number of patients with EAM were found in the age group of 46-60years

Male to female ratio was 1:2.9

The mean duration of disease was found to be 15.6years with maximum number of cases having disease duration between 11 and 20years

Anaemia of chronic disease was found to be the most common extra-articular manifestation found in this study. The other extra-articular manifestations noted in this were cardiac manifestations – 12%; ocular manifestations-18%; dermatological manifestation-24%

Pulmonary manifestation-27%; other-10%;overlap syndromes -6%

Rheumatoid factor was positive in 80% of patients in this study

SUMMARY

Rheumatoid arthritis is a chronic inflammatory disease of unknown etiology marked by a symmetric peripheral polyarthritis. It is a systemic disease .hence it may result in a variety of extra-articular manifestations including fatigue, subcutaneous nodule, lung involvement, pericarditis, peripheral neuropathy vasculitis and hematological abnormalities. The extra-articular manifestation may develop during the clinical course of rheumatoid arthritis even prior to the onset of arthritis. The patient most likely to develop extra-articular disease have a history of smoking early onset of significant physical disability and seropositivity of rheumatoid factor.

Extra-articular manifestations contribute significantly to the morbidity and mortality of rheumatoid arthritis. So careful screening of all patients for extra-articular manifestations may help reduce the same.

ANNEXURE1: BIBLIOGRAPHY

Pathophysiology:

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ANNEXURE-2

Proforma:

Biodata: Name: Age: Sex :	Sl no:
Address: Occupation:	
ACR/EULAR criteria: Score: Rheumatoid factor: Anti-CCP: ESR: CRP:	
Duration of the disease:	
Work up for extra-articular manifestations:	
1.Haematology: Complete hemogram: Peripheral smear:	Hb: TC: platelets:
2.Renal function test:	Urea: creatinine:
3.Serum electrolytes:	Sodium: Potassium:
4.Urine rountine:	
5.ECG:	
6.Chest X ray:	
7.Echocardiogram:	
8.USG abdomen&pelvis:	
9.HRCT chest:	
10.Pulmonary function test:	
11.Ophthalmological evaluation:	
12.ANA:	
13.Serum uric acid:	
FINAL DIAGNOSIS:	

ANNEXURE -3

CONSENT FORM

Yourself Mr./Mrs./Ms…….. are being asked to be a participant in the research study titled "A STUDY ON THE EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS" in CMC Hospital, Coimbatore, conducted by DR.PONMOZHI.G M.D., Post Graduate Student, Department of General Medicine, Coimbatore Medical College. You are eligible after looking into the inclusion criteria. You can ask any question you may have before agreeing to participate.

Research Being Done

A study on the extra-articular manifestations of rheumatoid arthritis

Purpose of Research

To investigate and compare the frequency and type of extra-articular manifestations

To correlate the number of extra-articular manifestations with the duration of the study

In a well defined community based cohort of patients with rheumatoid arthritis

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

---------- ----------

Signature /Left thumb impression Date

(volunteer)

---------- ----------

Signature of witness Date

ANNEXURE 4:

ஒப்புதல் படிவம்

பெயர் :

வயது :

பாலினம் :

முகவரி:

கோவை அரசு மருத்துவக்கல்லூரி மருத்துவமனையில் மருத்துவர் - தலைமையில் நடைபெறும் இந்த ஆய்வில் முழு சம்மதத்துடன் கலந்துகொள்ள சம்மதிக்கிறேன் .இந்த ஆய்வில் என்னை பற்றி விவரங்களை பாதுகாப்புடன் இந்த ஆய்வில் வெளியிட ஆட்சேபணை இல்லை என்று தெரிவித்துக் கொள்கிறேன் .எந்த நேரத்திலும் ஆய்வில் இருந்து எந்த நேரத்திலும் விலக்கிக்கொள்ளும் உரிமை உண்டு என்று அறிவேன் .

இடம் :

தேதி:

கைகெயாப்பம் /

ரேகை

ANNEXURE 5: MASTER CHART

S L .NO	NAME	AGE	SEX	RF	DURATION OF DISEASE	HEMATOLOGY	CARDIOLOGY	DERMATOLOGY	PULMONOLOGY	OPHTHALMOLOGY	OTHER	OVERLAP SYNDROMES
1	Radha Krishnan	56	M	+	23years	anaemia of chronic disease	-	-	-	-	-	-
2	Sangeetha	26	F	+	1year	-	-	-	-	-	-	-
3	Janaki	60	F	+	28years	-	-	-	-	-	-	-
4	Karuppathal	65	F	+	25years	Anaemia of Chronic disease	-	-	-	Episcleritis	-	-
5	Suganthy	38	F	+	12years	-	-	-	-	-	-	-
6	Mangammal	40	F	+	14years	-	-	-	-	-	-	-
7	Rangammal	58	F	+	14years	-	-	Mtxinduced mucositis	-	-	-	-
8	Chinnakutty	62	M	+	22years	-	-	-	-	-	-	-
9	Sandha	73	F	+	38years	Iron deficiency anemia, Neutropenia	Cardiac failure	-	Pulmonary fibrosis ,recurrent infections	-	-	-
10	Rajamani	39	F	+	11years	-	-	-	-	-	-	-
11	Krishnaveni	60	F	+	23years	Anemia of Chronic disease	-	-	-	Dry eye	-	-
12	Junaitha	30	F	+	5 years	-	-	-	-	-	-	-
13	Vijayalakshmi	47	F	-	7years	-	-	-	-	-	-	SLE Overlap
14	Nagamani	32	F	+	2years	-	-	Rheumatoid nodule	-	-	-	-
15	Pangajam	32	F	+	8 months	-	-	-	-	-	-	-
16	Shanmugasundaram	45	M	-	4 years	-	-	-	-	-	-	-
17	Suseela	36	F	+	3years	-	-	-	-	-	-	-
18	Paral	55	F	-	22years	Megaloblastic Anaemia	-	-	Pleural nodule	-	Distal polyneuropathy	-
19	Seethalakshmi	40	F	+	3years	-	-	-	-	-	-	-
20	Vasanthi	30	F	+	7years	-	-	-	-	-	-	-
21	Kamala	25	F	+	3years	-	-	-	-	-	-	-
22	Maragatham	58	F	+	20years	Thrombocytopenia, Eosinophilia	Pulmonary artery hypertension	-	ILD	-	-	-
23	Valarmathi	50	F	+	11years	-	-	-	-	-	-	-
24	Chinnaponnu	43	F	+	4years	-	-	Bilateral leg ulcers	-	-	-	-

25	Ponnamal	68	F	+	35years	Megaloblastic Anaemia	Cardiac failure, PAH	-	ILD	-	-	-
26	Manjula	29	F	+	2years	-	-	-	-	-	-	-
27	Loganayaki	40	F	+	5years	-	-	-	-	-	-	-
28	Velmurugan	46	M	+	16years	-	-	Small vessel vasculitis	-	-	-	-
29	Pattiyammal	47	F	+	12years	-	-	-	-	-	-	-
30	Nivetha	16	F	+	1year	-	-	-	-	-	-	-
31	Gowri	49	F	-	14years	-	-	-	-	-	-	-
32	Uma maheswari	38	F	+	4years	-	-	-	-	-	-	-
33	Maniyammal	45	M	+	13years	-	-	-	-	-	-	-
34	Karuppusamy	52	F	-	15years	-	-	-	Pleural effusion	-	-	-
35	Maheswari	45	F	+	11years	-	-	-	-	-	-	-
36	Nagarathinam	40	F	+	6years	-	-	-	-	-	-	-
37	Lakshmi	40	F	+	4years	-	-	Raynauds phenomenon	-	-	-	-
38	Sivagami	46	F	+	17years	Iron deficiency anaemia	-	-	-	-	-	-
39	Abdulla	50	F	+	13years	-	-	-	-	-	-	-
40	Maruthayi	51	F	+	2oyears	Iron Ydeficiency anaemia, Neutropenia	-	-	-	-	-	-
41	Pushpa	47	F	+	7years	-	-	-	-	-	-	-
42	Powjath	44	F	+	8years	-	-	-	-	-	-	-
43	Sujatha	32	F	-	2years	-	-	-	-	-	-	-
44	Vijaya	45	F	+	3years	-	-	Digital gangrene	-	Dry eye	-	-
45	Manimegalai	46	F	+	14years	-	-	-	-	-	-	-
46	Vishalani	31	F	+	2years	-	-	-	-	-	-	-
47	Arunachalam	58	M	+	12years	-	-	-	-	-	-	-
48	Palaniyammal	55	F	+	21years	Anaemia of Chronic disease	-	-	-	-	-	-
49	Bakiyalakshmi	34	F	+	3years	-	-	-	-	-	-	-
50	Sumithra	32	F	-	2years	-	-	-	-	-	-	-
51	Bakiyam	56	F	-	16years	-	-	-	-	-	-	-
52	Paneer selvam	55	M	+	11years	-	-	-	-	Dry eye	Mononeuritis multiplex	-
53	Selvarani	45	F	+	9years	-	-	-	-	-	-	-
54	Velusamy	56	M	+	14years	-	-	-	-	-	-	-
55	Ramasamy	64	M	+	23years	-	-	-	ILD,Respiratory failure	-	-	-
56	Gunasundhari	57	F	+	17years	-	Pericardial effusion	-	-	-	-	-
57	Thangavel	65	M	+	18years	-	-	-	-	-	-	-

58	Sekaran	65	M	+	12years	-	-	-	-	-	-	-
59	Shantha	45	F	+	13years	-	-	-	-	-	-	-
60	Muthulakshmi	45	F	-	4years	-	-	-	-	-	-	-
61	Nanjappa	62	M	+	12years	-	-	-	-	Dry eye	-	-
62	Rehala	54	F	-	8years	-	-	-	-	-	-	-
63	Hemapriya	30	F	+	3years	-	-	-	-	-	-	-
64	Velumani	43	M	+	11years	-	-	-	-	-	-	-
65	Rangammal	70	F	+	20years	-	-	Atrophic skin with purpura	-	-	-	-
66	Udayakumar	40	M	-	3years	-	-	-	-	-	-	-
67	Boopathy	38	M	+	8years	-	-	-	-	-	-	-
68	Fowsiya	27	F	+	1year	-	-	-	-	-	-	-
69	Brindha	18	F	+	1year	-	-	-	-	-	-	-
70	Kavitha	31	F	+	4years	-	-	-	-	-	-	-
71	Saroja	44	F	+	5years	-	-	-	-	-	-	-
72	Hakim	40	M	+	2years	-	-	-	-	-	-	-
73	Suyambukani	51	F	+	13years	-	-	Pyoderma gangrenosum	-	-	-	-
74	Usharani	50	F	+	14years	-	-	-	-	-	-	-
75	Shanthi	23	F	+	1year	-	-	-	-	-	-	-
76	Vasanthi	30	F	-	2years	-	-	-	-	-	-	-
77	Poongodi	54	F	+	13years	-	-	-	-	-	Drug induced UGI bleeding	-
78	Nagamanikam	30	F	+	2years	-	-	-	-	-	-	-
79	Ramasamy	45	M	+	11years	-	-	-	-	-	-	-
80	Lakshmi	50	F	+	17years	Anaemia of chronic disease, Thrombocytosis	-	-	-	Dry eye	-	-
81	Ambikadevi	38	F	+	2years	-	-	-	-	-	-	-
82	Pushpavalli	50	F	+	10years	-	-	-	-	-	-	-
83	Prema	32	F	-	2years	-	-	-	-	-	-	-
84	Rani	52	F	-	10years	-	-	-	Recurrent infections	-	-	-
85	Dhandapani	75	M	-	21years	Irondeficiency anaemia	-	-	-	-	-	-
86	Kuppurakathi	30	F	+	2years	-	-	-	-	-	-	-
87	Chinnal	47	F	+	12years	-	-	-	-	-	-	-
88	Saroja	60	F	+	14years	-	-	-	-	-	-	-
89	Susila	40	F	+	9years	-	-	-	-	-	-	Limited scleroderma overlap
90	Rani	45	F	+	10years	-	-	-	-	-	-	-
91	Kalaivani	50	F	+	8years	-	-	-	Eosinophilic pneumonia,	-	-	-

92	Jothimani	52	F	+	12years	-	-	-	-	-	-	-
93	Saroja	45	F	+	6years	Irondeficiency anaemia	-	-	-	-	-	-
94	Rajammal	57	F	+	8years	-	-	-	-	-	-	-
95	Chandrika	60	F	+	12years	-	-	-	-	-	-	-
96	Loganayaki	21	F	+	2years	-	-	-	-	-	-	-
97	Supriya	47	F	-	13years	-	-	-	-	-	-	-
98	Somasundaram	50	M	-	11years	-	-	-	-	-	-	-
99	Rukmani	58	F	+	9years	Anaemia of Chronic disease	-	-	-	-	-	-
100	Saradha	38	F	+	7years	-	-	-	Recurrent infections	-	-	-